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Original Investigation

Attentional and executive dysfunction as predictors of smoking within the Childhood Cancer Survivor Study cohort

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Abstract

Introduction: Previous research has suggested that childhood cancer survivors initiate smoking at rates approaching those of healthy individuals, even though smoking presents unique risks to survivors. The present study explores whether the attentional and executive functioning (EF) deficits associated with cancer and treatment place survivors of childhood cancer at increased risk for smoking.

Methods: Data from the Childhood Cancer Survivor Study were examined to identify concurrent and longitudinal correlates of tobacco use. We explored whether childhood attention problems and adulthood executive dysfunction were associated with smoking among adult survivors of childhood cancer.

Results: Childhood attention problems emerged as a striking predictor of adult smoking nearly a decade later on average. Nearly half (40.4%) of survivors who experienced attention problems in childhood reported a history of smoking, a significantly higher rate of ever smoking, than reported by those without childhood attention problems (relative risk [RR] = 1.53, 95% *CI* = 1.31–1.79). Furthermore, they were nearly twice as likely to be current smokers in adulthood compared with those without childhood attention problems (RR = 1.71, 95% *CI* = 1.38–2.11). Similar associations were found between components of adult executive dysfunction and adult smoking.

Discussion: Childhood cancer and treatment are associated with subsequent deficits in attention and EF. Early detection of these deficits will allow clinicians to identify patients who are at increased risk for smoking, an important step in promoting and maintaining health in this medically vulnerable population.

Introduction

As survival rates increase for childhood cancers, survivors must learn to make informed healthy decisions for prolonging their disease-free status. The decision to smoke is particularly problematic when considered in combination with the medical vulnerability survivors experience due to "late effects"—the lasting effects of disease and treatment. Survivors, regardless of smoking status, have more than a 10-fold increase in overall mortality risk compared with the U.S. population (Mertens et al., 2001), particularly related to secondary malignancy, cardiac events, and pulmonary disease.

Because of the risks associated with cancer and treatment, survivors of childhood cancer who smoke may incur substantially greater medical risk than their healthy peers who smoke. Nonetheless, there are no studies to date that directly examine the effects of smoking on the health outcomes or mortality rates of childhood cancer survivors. On the other hand, there is evidence that smoking is associated with the development of second malignancies (Johnson, 1998) and elevated morbidity among survivors of adult-onset cancer (Kawahara et al., 1998; Richardson et al., 1993). Furthermore, given that smoking appears to have a synergistic effect in the presence of other risk factors in the development of cardiovascular disease (Poulter, 1999), obesity, dys-

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lipidemia, hypertension, and other cardiovascular risk factors experienced by some survivors may be particularly threatening in conjunction with smoking.

Unfortunately, the medical vulnerability suffered by survivors does not appear to dictate smoking abstinence. Some studies report that smoking among childhood cancer survivors is less common than in controls or population comparisons (Demark-Wahnefried et al., 2005; Emmons et al., 2002; Frobisher et al., 2008; Tao et al., 1998), but other investigations have not detected group differences (Haupt et al., 1992; Hollen & Hobbie, 1993, 1996; Verrill, Schafer, Vannatta, & Noll, 2000). Among adult survivors of childhood cancer, prevalence rates range from 23% to 57% for trying cigarettes (Emmons et al.; Haupt et al.; Tao et al., 1998) and from 17% to 29% for current smoking (Emmons et al.; Haupt et al.; Larcombe, Mott, & Hunt, 2002; Meacham et al., 2005; Tao et al., 1998). In comparison with the general population, where an estimated 21% of adults are current smokers (Pleis, Lucas, & Ward, 2009), survivors of childhood cancer appear to be smoking at rates similar to their healthy peers. Clearly, a substantial minority of survivors chooses to engage in this unhealthy behavior despite their medical vulnerability. This is particularly alarming since some studies have found that survivors appear to be less likely than controls to successfully quit smoking once they are established smokers (Haupt et al.; Larcombe et al.; Tao et al., 1998).

Given the increased health risks that smoking is likely to impose on survivors of childhood cancer, it is important to consider what factors prompt survivors to smoke at rates similar to the general population. Little is known about the influence of cancer late effects on smoking behavior. Late effects involve lasting physical, cognitive, psychological, and social impairments that place survivors at risk for a range of complications. Connecting these late effects to health behavior decisions may illuminate important channels for prevention and intervention efforts.

Survivors of childhood cancer who received central nervous system (CNS) treatment (e.g., intrathecal chemotherapy, cranial radiation therapy [CRT]) are at risk for cognitive late effects, including deficits in attention, concentration, and executive functioning (EF; Anderson, Godber, Smibert, & Ekert, 1997; Fossen, Abrahamsen, & Storm-Mathisen, 1998; Holmquist & Scott, 2002; Langer et al., 2002; Lockwood, Bell, & Colegrove, 1999; Maddrey et al., 2005; Peterson et al., 2008; Rodgers, Horrocks, Britton, & Kernahan, 1999; Troy et al., 2000). The extent to which these lasting cognitive changes may impact health behavior decisions remains largely unexplored. Importantly, attention problem symptoms increase smoking risk within the general population (Fuemmeler, Kollins, & McClernon, 2007; Kollins, McClernon, & Fuemmeler, 2005; Tercyak, Lerman, & Audrain, 2002). Since survivors of childhood cancer often experience attention and EF problems posttreatment, affected survivors may have a vulnerability to smoking similar to that of their healthy peers with attention difficulties.

The present study is the first to examine the relationship between attentional/executive dysfunction and smoking in a sample of childhood cancer survivors. We hypothesized that (a) survivors with childhood attention problems would be more likely to smoke in adulthood, (b) executive dysfunction among adult survivors would be positively associated with smoking in adulthood, and (c) adult survivors with a history of CNS treatment would experience more symptoms of attentional/executive dysfunction, thus placing them at increased risk for smoking.

Methods

This study involved analysis of data collected for the Childhood Cancer Survivor Study (CCSS). The CCSS is a multiinstitutional collaboration examining long-term outcomes after childhood cancer. Beginning in 1994, data were collected through 26 clinical centers throughout the United States and Canada. Participants were patients diagnosed and treated at the clinical centers and who fulfilled the following eligibility criteria: (a) diagnosis of leukemia, CNS malignancy, Hodgkin's disease, non-Hodgkin's lymphoma, neuroblastoma, soft tissue sarcoma, kidney cancer, or bone cancer; (b) diagnosis between 1 January 1970 and 31 December 1986; (c) < 21 years of age at diagnosis; (d) alive 5-year postdiagnosis; (e) English or Spanish speaking; and (f) resident of the United States or Canada. Information is available on diagnosis, treatment, health, and quality of life outcomes for 14,372 survivors. Nearest-age siblings of randomly selected participants were invited to participate as comparison subjects. Detailed information about the CCSS study design and cohort characteristics has been published elsewhere (Robison et al., 2002).

The CCSS included medical chart abstractions of treatment from each participant's treating institution and periodic surveys of the survivor cohort. Data used in the present retrospective analysis were taken from surveys administered at two timepoints (baseline and the 2003 follow-up [2003FU]). Baseline surveys were distributed to survivors beginning in 1994. (To clarify, baseline does not refer to pretreatment measurement in this instance since participants were required to be at least 5-year postdiagnosis upon enrollment in the CCSS.) The 2003FU surveys were distributed to survivors from 2002 to 2005. The CCSS study documents and procedures were approved by the institutional review boards at each participating institution, and procedures for this retrospective analysis were approved by the University of Memphis and St. Jude Children's Research Hospital.

Participants

We examined both concurrent and longitudinal associations with smoking, requiring two separate subsamples for analysis. For the first hypothesis, participants were selected based on the following criteria: (a) <18 years old at baseline and (b) ≥18 years old at 2003FU (n = 2,022). These participants were > 10 years from diagnosis on average at baseline (M = 11.68, SD = 2.17). The mean time between baseline and 2003FU assessment was 8.12 years (SD = 0.93). A parent-report measure of attention problem symptoms at baseline was available for this subsample, which we then examined in relation to the participants' subsequent self-reported smoking behavior at 2003FU. For the second and third hypotheses, analysis included all participants who were aged 18 years or older at 2003FU (n = 8,383). These participants were 15–35 years from diagnosis at the time of 2003FU measurement (M = 23.68, SD = 4.54). We examined concurrent associations between executive dysfunction and smoking based on self-report at the 2003FU. Siblings aged ≥18 years old at 2003FU, with matching survivors from the executive dysfunction analysis, were used in a separate analysis of survivor/sibling pairs (n = 1,926 pairs). Follow-up surveys completed by proxies were excluded

from analysis. Demographic characteristics for survivors included in analyses addressing Hypotheses 1–2 are reported in Table 1.

Measures

Adult smoking status

Self-reported smoking status at follow-up was treated as a dependent variable. Participants were asked if they had ever smoked at least 100 cigarettes. This item was dichotomized into "ever-smokers" and "never-smokers." Participants were also asked if they currently smoke. From these data, a dichotomous variable identifying "current smokers" and "nonsmokers" was created.

Youth attention problems

Parental reports of youth attention problem symptoms at baseline were measured using four items from the Behavior Problems Index (BPI; Zill, 1990). Most BPI items were originally adapted from the Child Behavior Checklist (CBCL; Achenbach, 1991). The four BPI items of interest here were originally included on the Attention Problems Scale of the CBCL. These items produced a Cronbach's alpha of 0.76, indicating adequate internal consistency. Items were scored on a 3-point scale, with higher scores indicating more attention difficulties. The four items were then summed for an overall measure of attention problems. Survivors with scores falling within the highest 10th percentile of the sibling score distribution were defined as having "attention problems." All other participants were classified as having "no attention problems." This BPI scoring procedure was previously established with the CCSS cohort (Schultz et al., 2007). Similar BPI classification procedures have been used with other pediatric populations (Byrd, Weitzman, Lanphear, & Auinger, 1996; Gortmaker, Walker, Weitzman, & Sobol, 1990; McDermott, Mani, & Krishnaswami, 1995; McDermott et al., 1996) and have been found to reliably identify patients with mental health service referrals (Gortmaker et al.; McDermott et al., 1995, 1996). This procedure was not intended to yield a sample that would meet diagnostic criteria for attention-deficit/hyperactivity disorder but allowed comparison between participants with relatively high and low reports of symptoms.

Adult executive dysfunction

At 2003FU, adult participants rated their own behavior on a measure of EF called the CCSS–Neurocognitive Questionnaire (CCSS-NCQ; Krull et al., 2008). This measure includes 19 items adapted from the Behavior Rating Inventory of Executive Function (Guy, Isquith, & Gioia, 1996), an instrument frequently used in clinical contexts to assess symptoms of attentional/executive dysfunction. The CCSS-NCQ yields four empirically derived factors: task efficiency (attention and processing speed), organization (organizational functioning), emotional regulation (emotional reactivity and tolerance for frustration), and memory (working and long-term memory). Participants rated items on a 3-point scale ranging from *never a problem* to *often a problem*. Using a scoring paradigm established in a validation study (Krull et al.), participants were classified as *high risk for executive dysfunction* in a given domain if any response in that domain indicated *often a problem*. All other participants were considered to have *no executive dysfunction*.

Independent variables

Baseline surveys provided demographic information. Diagnosis and treatment-related information was available from medical chart abstractions from the treating institutions. Initially, we examined several categories of CNS treatment associated with cognitive late effects, including CRT, certain intrathecal and high-dose chemotherapies (e.g., methotrexate, cytosine arabinoside [Ara-C]), dexamethasone, brain surgery, and combinations of these treatments. However, CRT emerged as the only treatment group significantly associated with smoking. Thus, the treatment variable was simplified into a dichotomous variable (CRT and no CRT) for the analyses presented here. Additionally, due to the high correlation between diagnosis and treatment variables, we included treatment, but not diagnosis, in our analyses because treatment was critical to our mediation hypothesis. These variables were included as covariates in analyses.

Data analyses

Multivariate generalized linear models were used to examine relationships between our dependent measure (smoking status) and our primary predictors and covariates. Because smoking was a common outcome (~30%) for our cohort, relative risks (RRs) were calculated directly based on a generalized linear model with a log link function and Poisson distribution with robust error variances (Zou, 2004). For each dependent measure, a model saturated with all predictor terms was developed. Nonsignificant predictor terms were then removed until all remaining terms were statistically significant at $p < .05$. RRs and 95% *CI*s are reported. For comparisons between survivors and siblings, conditional logistic regression models were used to calculate odds ratios (*OR*s) for each smoking, attention, and EF measure, adjusting for gender and age. The specific analytic approach for each hypothesis is outlined below.

1. Youth attention problems at baseline were used to predict adult smoking status at 2003FU (n = 2,022). Comparisons were also made between available survivor–sibling pairs (n = 692 pairs) to explore occurrence rates of attention problems between groups while adjusting for intra-family contributions to the likelihood of smoking.
2. The cross-sectional relationship between adult executive dysfunction and adult smoking status at 2003FU was examined among survivors (n = 8,383). Comparisons were also made between available survivor–sibling pairs (n = 1,926 pairs) to adjust for familial contributions to EF–smoking relationships.
3. We also hypothesized that executive dysfunction mediates the relationship between treatment and smoking. A series of regression models were carried out to test if (a) treatment significantly predicted smoking, (b) treatment significantly predicted executive dysfunction, and (c) executive dysfunction significantly predicted smoking when treatment was controlled (Baron & Kenny, 1986). If all relationships were found to be significant, these analyses would be followed by a Sobel test to determine the significance of the mediation effect (Preacher & Hayes, 2004).

Results

Youth attention problems and smoking in adulthood

Characteristics of smokers examined in Hypothesis 1 are reported in Table 2. Attention problems in childhood were identified

Table 1. Demographic and cancer-related characteristics of survivors for testing Hypotheses 1–2

	Number of survivors (%)	
	Age <18 years at baseline and age ≥18 years at 2003FU (Hypothesis 1)	Age ≥18 years at 2003FU (Hypothesis 2)
Total *n*	2,022	8,383
Sex		
Female	1,068 (52.8)	4,252 (50.7)
Male	954 (47.2)	4,131 (49.3)
Race/ethnicity[a]		
White, non-Hispanic	1,701 (84.1)	7,178 (85.6)
Non-White	311 (15.4)	1,172 (14.0)
Cancer diagnosis		
Bone cancer	20 (1.0)	738 (8.8)
CNS	200 (9.9)	887 (10.6)
Hodgkin's disease	17 (0.8)	1,142 (13.6)
Kidney (Wilms)	369 (18.2)	792 (9.4)
Leukemia	924 (45.7)	2,860 (34.1)
Non-Hodgkin's lymphoma	77 (3.8)	652 (7.8)
Neuroblastoma	295 (14.6)	549 (6.5)
Soft tissue sarcoma	120 (5.9)	763 (9.1)
Cancer treatment[b]		
CRT	528 (26.1)	2,315 (27.6)
IT MTX	894 (44.2)	2,838 (33.9)
HD Ara-C	432 (21.4)	1,185 (14.1)
HD MTX	196 (9.7)	810 (9.7)
Spinal radiation	121 (6.0)	575 (6.9)
Brain surgery	182 (9.0)	797 (9.5)
Dexamethasone	196 (9.7)	574 (6.8)
Age at baseline (years)		
M (*SD*)	14.2 (2.2)	23.9 (7.7)
Range	8–17	8–48
Age at 2003FU (years)		
M (*SD*)	22.3 (2.2)	31.6 (7.5)
Range	18–27	18–54
Age at cancer diagnosis (years)		
M (*SD*)	2.5 (1.9)	8.0 (5.8)
Range	0–9	0–20

Note. 2003FU = 2003 follow-up; CNS = central nervous system; CRT = cranial radiation therapy; HD = high dose (≥1,000 mg/m^2); IT = intrathecal; MTX = methotrexate.

[a]Missing race information: Hypothesis 1 (n = 10) and Hypothesis 2 (n = 33).

[b]Some survivors are represented in more than one treatment category. Missing treatment information for survivors without medical chart abstractions: Hypothesis 1 (n = 124) and Hypothesis 2 (n = 706).

in 15% of survivors. In this subsample, 30% reported ever smoking, while 19% reported current smoking at 2003FU.

We examined the longitudinal relationship between youth attention problems and both adult ever smoking and adult current smoking. RRs and *CI*s are reported in Table 3. Results indicated that survivors with attention problems in childhood were significantly more likely to be ever-smokers as adults than those without attention problems (RR = 1.53, 95% *CI* 1.31–1.79). Similarly, current smoking in adulthood was nearly twice as likely (RR = 1.71, 95% *CI* 1.38–2.11) among survivors with attention problems in childhood compared with those without attention problems. Both of these associations persisted even after controlling for statistically significant covariates. Additionally, survivors who reported either ever or current smoking were more likely to be men, older at time of follow-up, and/or without a history of CRT. Ever smoking was also more likely among White participants.

Data were available on the siblings of a subset of survivors. We compared the occurrence of attention problem symptoms between sibling and survivor pairs. Increased parental report of childhood attention problems for survivors compared with siblings approached statistical significance (*OR* = 1.40, 95% *CI* 0.97–2.01, p = .07), adjusting for age and gender. This trend is generally consistent with our expectation that survivors of childhood cancer, at risk for cognitive late effects, exhibit more attention problem symptoms than healthy age-mates.

Table 2. Characteristics of smokers among 2,022 survivors (Hypothesis 1[a])

	Number of survivors	Number of smokers (%)[b]	
		Ever-smokers	Current smokers
Total subsample	2,022	609 (30.1)	386 (19.1)
Sex			
Female	1,068	286 (26.8)	179 (16.8)
Male	954	323 (33.9)	207 (21.7)
Race/ethnicity[c]			
White, non-Hispanic	1,701	534 (31.4)	335 (19.7)
Non-White	311	75 (24.1)	51 (16.4)
Age at diagnosis (years)			
0–2	1,101	287 (26.1)	183 (16.6)
3–5	761	255 (33.5)	161 (21.2)
6–9	160	67 (41.9)	42 (26.3)
Age at 2003FU (years)			
18–20	474	98 (20.7)	62 (13.1)
21–22	559	168 (30.1)	112 (20.0)
23–24	612	185 (30.2)	116 (19.0)
25–27	377	158 (41.9)	96 (25.5)
Cancer diagnosis			
Bone cancer	20	5 (25.0)	1 (5.0)
CNS	200	46 (23.0)	25 (12.5)
Hodgkin's disease	17	5 (29.4)	4 (23.5)
Kidney (Wilms)	369	119 (32.2)	77 (20.9)
Leukemia	924	265 (28.7)	177 (19.2)
Non-Hodgkin's lymphoma	77	34 (44.2)	22 (28.6)
Neuroblastoma	295	93 (31.5)	57 (19.3)
Soft tissue sarcoma	120	42 (35.0)	23 (19.2)
Cancer treatment[d]			
CRT	528	119 (22.5)	82 (15.5)
IT MTX	894	272 (30.4)	180 (20.1)
HD Ara-C	432	113 (26.2)	76 (17.6)
HD MTX	196	61 (31.1)	42 (21.4)
Spinal radiation	121	22 (18.2)	18 (14.9)
Brain surgery	182	42 (23.1)	22 (12.1)
Dexamethasone	196	51 (26.0)	33 (16.8)
Youth attention problems[c]			
No	1,680	475 (28.3)	294 (17.5)
Yes	302	122 (40.4)	84 (27.8)

Note. 2003FU = 2003 follow-up; CRT = cranial radiation therapy; HD = high dose (≥1,000 mg/m^2); IT = intrathecal; MTX = methotrexate; .

[a]Study population defined as those <18 years of age at baseline and ≥18 years of age at 2003FU (n = 2,022).

[b]Number (%) = participants in the row who are ever- or current smokers.

[c]Missing information: race (n = 10) and youth attention problems (n = 40).

[d]Some survivors are represented in more than one treatment category. Treatment information is missing for survivors without medical chart abstractions (n = 124).

Executive dysfunction and smoking in adulthood

Characteristics of smokers examined in Hypothesis 2 are reported in Table 4. EF problems were identified in 14%–20% of this subsample across domains. With 32% of survivors reporting ever smoking and 16% reporting current smoking at 2003FU, smoking rates in this subsample were comparable with the rates identified in the subsample used to test Hypothesis 1.

Table 3. Poisson regression results of youth attention problems, demographic, and disease/treatment-related variables for adult smoking status (Hypothesis 1)

	RR (95% *CI*)	
Variables	Ever-smokers[a]	Current smokers[b]
History of CRT		
Yes	1.0	1.0
No	1.59 (1.34–1.90)*	1.45 (1.16–1.82)*
Youth attention problems		
No	1.0	1.0
Yes	1.53 (1.31–1.79)*	1.71 (1.38–2.11)*

Note. CRT = cranial radiation therapy; RR = relative risk. All models were adjusted for age at 2003 follow-up, age at diagnosis, gender, and race. RRs of 1.0 indicate the reference group for categorical variables.

[a]n = 1,826 observations in the model for ever-smokers.

[b]n = 1,819 observations in the model for current smokers.

*$p < .01$.

We examined the concurrent relationship between adult executive dysfunction and both adult ever smoking and adult current smoking. RRs and *CI*s are reported in Table 5. Results indicated that adult survivors with dysfunction in specific domains of EF were at risk for smoking. Specifically, survivors with dysfunction in memory and emotional regulation were significantly more likely to have tried smoking in the past compared with those without executive dysfunction (RR = 1.25, 95% *CI* 1.12–1.39 and RR = 1.26, 95% *CI* 1.15–1.39, respectively), even after controlling for significant demographic and disease/treatment-related variables. Ever-smokers were also more likely to be men, older at time of follow-up, and/or without a history of CRT. Adult survivors experiencing memory and emotional regulation dysfunction were also more likely to be current smokers than those without executive dysfunction (RR = 1.23, 95% *CI* 1.04–1.45 and RR = 1.43, 95% *CI* 1.23–1.66, respectively), even after controlling for significant covariates. Survivors who reported current smoking were more likely to be White and/or without a history of CRT. No other significant differences were found.

Data were available on the siblings of a subset of survivors to provide an exploration of the smoking–attention relationships while adjusting for familial contributions. Survivors were more likely to experience executive dysfunction than their siblings (memory *OR* = 2.00, 95% *CI* 1.04–3.83 and task efficiency *OR* = 2.12, 95% *CI* 1.19–3.79). In contrast, survivors were less likely to try smoking (*OR* = 0.50, 95% *CI* 0.42–0.59) and less likely to smoke regularly (*OR* = 0.57, 95% *CI* 0.47–0.71) compared with siblings. Notably, the relations between EF dysfunction and smoking identified among survivors were not found among siblings. In fact, no associations were found between EF factors and current sibling smoking. Only memory dysfunction was associated with ever smoking among siblings after controlling for age, gender, and race (RR = 1.67, 95% *CI* 1.22–2.29).

Table 4. Characteristics of smokers among 8,383 survivors (Hypothesis 2[a])

	Number of survivors	Number of smokers (%)[b]	
		Ever-smokers	Current smokers
Total subsample	8,383	2,709 (32.3)	1,345 (16.0)
Sex			
Female	4,252	1,283 (30.2)	623 (14.7)
Male	4,131	1,426 (34.5)	722 (17.5)
Race/ethnicity[c]			
White, non-Hispanic	7,178	2,358 (32.9)	1,164 (16.2)
Non-White	1,172	344 (29.4)	176 (15.0)
Age at diagnosis (years)			
0–2	1,862	541 (29.1)	304 (16.3)
3–5	1,873	577 (30.8)	328 (17.5)
6–9	1,370	441 (32.2)	228 (16.6)
10–15	2,144	713 (33.3)	326 (15.2)
16–20	1,134	437 (38.5)	159 (14.0)
Age at 2003FU (years)			
18–24	1,722	478 (27.8)	313 (18.2)
25–29	1,767	598 (33.8)	304 (17.2)
30–34	1,946	587 (30.2)	293 (15.1)
35–39	1,553	499 (32.1)	235 (15.1)
40–54	1,395	547 (39.2)	200 (14.3)
Cancer diagnosis			
Bone cancer	738	259 (35.1)	122 (16.5)
CNS	887	250 (28.2)	124 (14.0)
HD	1,142	436 (38.2)	162 (14.2)
Kidney (Wilms)	792	272 (34.3)	144 (18.2)
Leukemia	2,860	830 (29.0)	470 (16.4)
Non-Hodgkin's lymphoma	652	228 (35.0)	114 (17.5)
Neuroblastoma	549	189 (34.4)	101 (18.4)
Soft tissue sarcoma	763	245 (32.1)	108 (14.2)
Cancer treatment[d]			
CRT	2,315	573 (24.8)	337 (14.6)
IT MTX	2,838	815 (28.7)	457 (16.1)
HD Ara-C	1,185	322 (27.2)	158 (13.3)
HD MTX	810	234 (28.9)	116 (14.3)
Spinal radiation	575	136 (23.7)	82 (14.3)
Brain surgery	797	221 (27.7)	107 (13.4)
Dexamethasone	574	151 (26.3)	73 (12.7)
EF			
Task efficiency problem			
No	4,562	1,372 (30.1)	614 (13.5)
Yes	1,709	559 (32.7)	299 (17.5)
Organization problem			
No	5,129	1,564 (30.5)	715 (13.9)
Yes	1,142	367 (32.1)	198 (17.3)
Emotional regulation problem			
No	4,759	1,376 (28.9)	609 (12.8)
Yes	1,512	555 (36.7)	304 (20.1)
Memory problem			
No	5,061	1,494 (29.5)	687 (13.6)
Yes	1,210	437 (36.1)	226 (18.7)

Note. 2003FU = 2003 follow-up; CNS = central nervous system; CRT = cranial radiation therapy; EF = executive functioning; HD = high dose (≥1,000 mg/m^2); IT = intrathecal; MTX = methotrexate.

[a]Study population defined as those ≥18 years of age at 2003FU (n = 8,383).

[b] Number (%) = participants in the row who are ever- or current smokers.

[c]Missing information: race (n = 33) and EF (n = 2,112).

[d]Some survivors are represented in more than one treatment category. Treatment information is missing for survivors without medical chart abstractions (n = 706).

Table 5. Poisson regression results of adult attention problems, demographic, and disease/treatment-related variables for adult smoking status (Hypothesis 2)

Variables	RR (95% *CI*) Ever-smokers[a]	Current smokers[b]
History of CRT		
Yes	1.0	1.0
No	1.47 (1.33–1.62)*	1.28 (1.10–1.48)*
Executive functioning		
Task efficiency problem		
No	1.0	1.0
Yes	1.03 (0.93–1.14)	1.09 (0.93–1.29)
Organization problem		
No	1.0	1.0
Yes	0.91 (0.82–1.02)	1.02 (0.87–1.21)
Emotional regulation problem		
No	1.0	1.0
Yes	1.26 (1.15–1.39)*	1.43 (1.23–1.66)*
Memory problem		
No	1.0	1.0
Yes	1.25 (1.12–1.39)*	1.23 (1.04–1.45)*

Note. CRT = cranial radiation therapy; RR = relative risk. All models were adjusted for age at 2003 follow-up, age at diagnosis, gender, and race. RRs of 1.0 indicate the reference group for categorical variables.

[a] $n = 5{,}779$ observations in the model for ever-smokers.

[b] $n = 5{,}673$ observations in the model for current smokers.

*$p < .05$.

Cancer treatment, executive dysfunction, and smoking in adulthood

Given these findings, we were interested in determining whether executive dysfunction mediates the association between treatment and smoking. Results of the first step of model testing did not support our hypothesis. CRT was not found to be a risk factor for smoking when compared with no CRT. A history of CRT was consistently associated with decreased smoking risk, as has been reported elsewhere (Emmons et al., 2002). No other treatment group differences were identified. Still, in the other two steps of conventional mediation testing, we determined the following: (a) Survivors previously treated with CRT were significantly more likely to experience executive dysfunction as adults in the domains of emotional regulation (RR = 1.27, 95% *CI* 1.10–1.47), task efficiency (RR = 2.01, 95% *CI* 1.80–2.25), and memory (RR = 1.90, 95% *CI* 1.66–2.17) and (b) survivors with executive dysfunction were more likely to be smokers (reported above).

Discussion

With improving success treating childhood cancers, the promotion of healthy behaviors within the growing survivor population is an emergent priority. The late effects of disease and treatment present unique challenges to survivors that can affect functioning, health, and long-term survival. To our knowledge, this is the first study to examine the relationship between possible cognitive late effects and smoking in a sample of childhood cancer survivors. Results demonstrated strong concurrent and longitudinal associations between attentional/executive dysfunction and smoking. Childhood attention problems emerged as a striking predictor of adult smoking close to a decade later on average. Nearly half of the survivors who experienced attention problems in childhood reported having smoked as adults. Furthermore, they were almost twice as likely to be current smokers in adulthood compared with survivors without attention problems. Similar associations were found between adult executive dysfunction and adult smoking.

While the mechanism underlying the associations between smoking and attention/EF in survivors remains unclear, there are reasonable possibilities warranting further study. In the general population, the association between attention problems and smoking behavior is often explained in terms of a self-medication model in which smokers benefit from the stimulant property of nicotine by experiencing enhanced attention and concentration. This model is supported by clinical and laboratory studies showing improvement on cognitive and behavioral measures of attention after nicotine administration in both clinical (Levin, Conners, Silva, Canu, & March, 2001; Levin & Rezvani, 2000; Levin et al., 1996; Potter & Newhouse, 2004) and nonclinical samples (Ernst, Heishman, Spurgeon, & London, 2001; Levin et al., 1998).

Following this conceptualization, childhood cancer survivors who experience certain cognitive late effects may have a vulnerability to smoking similar to their healthy peers with attention problem symptoms. This similarity may have important implications for health promotion in this medical population. Survivors have demonstrated improvements in attentional and behavioral functioning on methylphenidate trials (Conklin et al., 2007; Mulhern et al., 2004; Thompson et al., 2001), increasing the clinical use of stimulants for posttreatment attentional deficits. If stimulant therapy reduces or renders inconsequential the attention-enhancing benefits of nicotine, treating survivors' cognitive symptoms may also reduce their smoking risk.

Our findings identified two components of EF (emotion regulation and memory) associated with smoking. Smoking to regulate emotion (e.g., for managing stress) is a common "benefit" reported by smokers and often serves as a stumbling block for smokers trying to quit (Kassel, Stroud, & Paronis, 2003). The significant association between smoking and the EF–memory factor (including both working and long-term memory) is intriguing in light of the research on attention and tobacco in the general population. Some survivors may smoke for the stimulant benefit they experience for daily tasks requiring mental manipulation of information stored in immediate memory (e.g., calculating a sale price). Alternatively, survivors with memory problems may have more difficulty recalling and applying information related to their disease and treatment history when making health behavior decisions, such as choosing whether to try cigarettes. Further study of how attentional/EF deficits influence survivors' smoking decisions may guide intervention.

We hypothesized that certain cancer treatments contribute to deficits in attention and EF, which leave survivors at increased risk for smoking; however, this mediation model was not fully supported by formal model testing. Contrary to our proposed model, a history of CRT decreased smoking risk in our subsamples, a finding that is consistent with previous CCSS findings

(Emmons et al., 2002). Still, survivors who were exposed to CNS treatment exhibited more attentional/EF problems than those without such a treatment history. Furthermore, survivors with attention problems and executive dysfunction were more likely to smoke. As such, important components of the model were supported, although the data did not conform to the mediation model as a whole. Of note, we were unable to differentiate between attentional/EF problems experienced as a consequence of treatment and those from a developmental etiology in this sample. Therefore, treatment may have explained executive dysfunction in only a subset of our sample, obscuring detection of a mediation effect. Future investigations should control for developmental attentional/EF difficulties to help clarify the role of CRT in the onset of smoking among survivors.

Comparison between sibling and survivor pairs allowed exploration of the uniqueness of the survivorship context in the EF–smoking relationship. As expected, survivors exhibited more executive dysfunction than their siblings. Although survivor smoking rates were lower compared with siblings, executive dysfunction assumed a stronger role in the smoking behavior of survivors. This finding may indicate that cognitive late effects posttreatment have a unique influence on the smoking decisions of survivors that may leave affected survivors particularly vulnerable to making dangerous health behavior decisions. Just as treatment for cancer places survivors at subsequent medical risk, it seems that posttreatment cognitive late effects could place survivors at risk for smoking, a behavior that is certain to further endanger disease-free status. Although notable differences emerged between siblings and survivors, we are unable to assume causality with available data, particularly in terms of the cause (developmental or treatment-related) of attention and EF problems among survivors.

Importantly, factors other than the cognitive constructs examined here appear to influence the smoking behaviors of survivors who received CRT. Although our analyses included many important demographic and disease/treatment-related covariates, social environmental factors that may influence survivors' smoking decisions were not examined in the current study. Social influences, such as parent and peer smoking, have been demonstrated to influence attitudes about smoking as well as predict onset and progression among healthy adolescent smokers (Flay et al., 1994; Wang, Fitzhugh, Westerfield, & Eddy, 1995). Tyc, Lensing, Kolsky, Rai, and Robinson (2005) reported that social influences appeared to similarly affect tobacco outcomes in adolescents with cancer when compared with those without cancer. Therefore, a limitation of this study is that it cannot address the relative increase in risk for smoking due to attention problems relative to social influences among survivors. Future studies should examine the relative contribution of these variables to smoking behaviors among young cancer survivors.

While it seems unlikely that CRT protects survivors from smoking, patients who received CRT may experience a unique social environment that does not support smoking. Brain tumor survivors, a large proportion of the participants who received CRT in our sample, are at particular risk for a range of functional impairments posttreatment, including cognitive, educational, social, and medical disabilities (Butler & Mulhern, 2005; Hays et al., 1992; Hudson et al., 2003; Mertens et al., 2001; Mitby et al., 2003; Patenaude & Kupst, 2005; Zebrack et al., 2004). As a group, these survivors may occupy social environments that protect them from smoking initiation (e.g., social isolation limits smoking offers from peers). Thus, attentional/EF deficits may never contribute to smoking onset because the opportunity for smoking is absent. Interestingly, although survivors treated with CRT may be less likely to initiate smoking, they have more difficulty quitting once they are established smokers than other survivors (Emmons et al., 2002; Tao et al., 1997), clearly demonstrating the importance of prevention over intervention with this population.

There are important limitations that accompany retrospective analysis of preexisting datasets that should be considered when interpreting these findings. Most notably, we were limited in terms of our ability to quantify our constructs of interest. In particular, identification of attention and EF problems was based on available questionnaire items with non-normative cutoff scores to define symptomatic groups. Without performance-based assessment of these abilities for comparison, it remains unclear the extent to which our classifications correctly identify survivors with clinically significant attentional difficulty. Still, significant associations between smoking and attention problem symptoms in nonclinical, population-based, and community samples have been reported (Fuemmeler et al., 2007; Kollins et al., 2005; Rodriguez, Tercyak, & Audrain-McGovern, 2008; Tercyak et al., 2002). Even if the entirety of our attention problems group does not experience clinically concerning impairment in daily functioning, our findings still indicate that survivors exhibit more attention problem symptoms than healthy siblings and these symptoms place them at risk for smoking. Identification of these relations despite these measurement concerns suggests that we have determined areas needing further study where more comprehensive validated measurement would be possible and appropriate.

Findings are also limited by the restricted scope of this study. Using the data available through the CCSS, we were unable to assess other factors known to influence smoking behavior, namely family and peer smoking. Sibling smoking rates were helpful for comparison, but the social contribution to survivor smoking could not be fully explored here. Also, we did not have data available to determine the onset of survivor attention problems for comparison with the time of diagnosis and treatment. While posttreatment cognitive changes are well documented in the survivor literature and rates of attention problems among survivors exceeded those identified in the sibling group in this study, we are unable to determine whether survivor attention problem symptoms were treatment related or developmental in etiology. As such, it is unclear if the relation between smoking and attention problems identified in this study simply mirrors findings in the general population. Even so, better understanding of the factors that influence survivors to smoke is essential to inform prevention efforts—even if we learn that survivors smoke, despite their increased medical risk, for the very same reason as their healthy peers.

Often, survivor research is limited by small sample size. Fortunately, we were able to use data from the comprehensive CCSS, providing samples large enough to control for many potential covariates (e.g., diagnosis, treatment history). This study employed a unique approach to examining health behavior from within the context of survivorship. A concerning number of childhood cancer survivors choose to smoke despite their medical history and associated risks. The clinical implications are clear: Health care providers should recognize that cognitive

symptoms experienced in childhood place survivors at risk for smoking as adults. Early detection of deficits in attention and EF should allow clinicians to identify patients who are at increased risk for smoking, an important step in promoting and maintaining health in this medically vulnerable population.

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Declaration of Interests

None declared.

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