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Substance Use Among Young Adult Survivors of Childhood Cancer With Cognitive Impairment: An Analysis of the Project Forward Cohort

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abstract

PURPOSE Young adult childhood cancer survivors (YACCSs) are often impacted by cancer-related cognitive impairment (CRCI) and psychological distress. Using the Project Forward Cohort, we evaluated the relationship between CRCI and substance use behaviors.

METHODS YACCSs were surveyed between 2015 and 2018 (N = 1,106, female = 50.8%, Hispanic = 51.5%, median age = 25.5 years). Associations between CRCI and substance use (tobacco, binge drinking, marijuana, prescription drug misuse, and e-cigarette/vaporizer) were examined in multivariate logistic or log-binomial regressions, adjusting for child at diagnosis (0-14 years), years since diagnosis, sex, race/ethnicity, cancer type, and treatment intensity. Mediation analysis was performed to determine opportunities for interventions.

RESULTS CRCI was reported by 144 (13.0%) survivors. The highest prevalence was observed in CNS cancers (25.4%) and leukemia (13.3%) survivors. After covariate adjustment, CRCI was associated with 2.26 times the odds of prior 30-day vaping (95% CI, 1.24 to 4.11; $P = .007$). Mediators with significant indirect effects in the CRCI-vaping relationship include depressive symptoms (Center for Epidemiological Studies Depression Scale) and having two or more cancer-related late effects ($P < .05$).

CONCLUSION CRCI among YACCSs was associated with reports of vaping. Oncologists should screen for vaping behavior if CRCI is apparent. Increasing access to long-term follow-up clinics, addressing physical and mental health issues, and monitoring and educating on vaping and other substance use behaviors is recommended to improve the long-term health of YACCSs.

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INTRODUCTION

The reported prevalence of cancer-related cognitive impairment (CRCI) ranges between 10% and 40% across different neurocognitive domains among childhood, adolescent, and young adult patients with cancer,[1-3] and it is more prominent among those diagnosed with central nervous system (CNS) malignancies and leukemia.[1,4] Key insults leading to CRCI have been identified as cancer itself, especially with CNS tumors, as well as anticancer treatments such as cranial radiation and intrathecal chemotherapy.[4] Concurrent emotional and social dysfunction is observed with cognitive impairment, with afflicted survivors reporting higher risks of unemployment, not attaining a college degree, and dependent living.[1,2,5] As CRCI may persist up to 20 years after cancer diagnosis among childhood cancer survivors,[6] young adult childhood cancer survivors (YACCSs, 15-39 years) are at risk experiencing developmental problems compared with their peers. While survivorship care providers will monitor neurocognitive issues during follow-up care visits, there remains a lack of effective interventions to manage CRCI in cancer survivorship.[7-9]

Alcohol use, cigarette use, and drug use are risky lifestyle behaviors that are recommended for monitoring during survivorship care of young cancer survivors as they are frequently linked to poor health outcomes.[9,10] Known predictors of smoking initiation and alcohol consumption include psychological and emotional distress, which are associated with CRCI.[7,11,12] Hence, there is potential for higher risks of substance use among CRCI-affected survivors which may indicate greater need for close monitoring of these behaviors during follow-ups on the basis of

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recommendations in the Children's Oncology Group.[9] Substance use behaviors may also have a negative impact on cognition which indicates the possibility of a cycle of worsening in the cognition-substance use relationship.[13,14] To our knowledge, however, this relationship is yet to be explored in YACCSs.

By using a hypothesis-generating approach, this study investigated the association between CRCI and substance use behaviors in the Project Forward Cohort,[15] a population-based and ethnically diverse sample of YACCSs diagnosed in Los Angeles County. Through a secondary analysis of existing data, correlates of CRCI were examined to verify the classification of participants with CRCI in the study data set. Additionally, we performed a mediation analysis to identify important health and psychosocial mediators that could be intervened so as to reduce substance use behaviors that were associated with CRCI.

METHODS

Data Source

Potential participants were identified from the Los Angeles Cancer SEER Cancer Registry. Inclusion criteria included (1) diagnosis with any cancer (stage II or greater and all stages for the brain) during 1996-2010, (2) age 0-19 years at diagnosis, (3) residence in Los Angeles County, and (4) at least 5 years having passed since diagnosis. All recruited subjects provided active consent for participation, and the research protocol was approved by the California State Committee for the Protection of Human Subjects, the California Cancer Registry, and the Institutional Review Board at the University of Southern California (No. HS-14-00817). The study procedures have been described previously.[15] A total of 1,106 subjects completed the survey between 2015 and 2018 and were included in the analysis. Key measures were identified from both self-reported survey data and cancer registry data. The sources (survey or registry) with survey questions (if applicable) for each measure are summarized in the Data Supplement (online only).

Measures

Self-reported CRCI. We defined participants as having self-reported CRCI (yes, no) if they reported having difficulties with learning and memory as a problem at the time of survey.

Substance use behavior. Substance use (cigarette use, binge drinking, marijuana, prescription drug misuse, and e-cigarette/vaporizer use) was defined by any reported use (yes, no) in the prior 30 days. Binge drinking was defined by having five or more drinks of alcohol on a single occasion (within a couple of hours). Prescription drug misuse was determined by the use of (any) prescription drugs not prescribed by a physician. The e-cigarette/vaporizer use question was added after initial study launch (with 71 participants missing this item).

Demographic and clinical factors. Demographic information included age at survey, age at diagnosis, years since diagnosis, sex, race/ethnicity, education level, insurance, employment, and socioeconomic status (SES). Quintiles of SES were estimated with an area-based composite index computed using socioeconomic factors (education, occupation, employment, household income, poverty, rent, and house valuations) from census sources.[16-18] Cancer registry data contributed the SES, cancer type, age at diagnosis, and ethnicity.

Treatment intensity was determined using the Intensity of Treatment Rating Scale 3.0 with cancer registry data such as cancer diagnosis and initial therapy received.[19,20] The validation of the methodology against chart-abstracted data has been published elsewhere.[19] There were four levels of intensity from level 1 (least intensive) to level 4 (most intensive).[20] Participants were asked (yes/no) whether they were experiencing cancer-related late effects at the time of survey (inability to have children, heart problems, second cancer, weight gain, liver damage, hearing problems, lung problems, poor eyesight, sexual functioning problems, and bone fractures). A summative score ranging from 0 to 10 was generated for each participant by adding up each reported late effect for all participants.

Psychosocial variables. Depressive symptoms were assessed with the 20-item Center for Epidemiological Studies Depression Scale (CES-D).[21] The questionnaire queries about the frequency of experiencing depressive symptoms in the previous week on a 4-point Likert scale (1 = rarely or none of the time [< 1 day], 2 = some or a little of the time [1-2 days], 3 = occasionally or a moderate amount of the time [3-4 days], and 4 = most or all of the time [5-7 days]). A total score was calculated in the range of 0 to 46, and higher scores represent more depressive symptoms (α = .906).

Post-traumatic growth was evaluated with an 11-item modified Post-Traumatic Growth Inventory that has been previously administered in patients with cancer.[22] Items ask about the degree of positive and negative changes in different aspects of life as a result of cancer (eg, priorities in life, self-appreciation, compassion for others, handling difficulties, and spirituality), using a 5-point scale (1 = highly negative change, 2 = somewhat negative change, 3 = no change, 4 = somewhat positive change, and 5 = highly positive change). A total mean score was calculated, with higher scores representing more post-traumatic growth (α = .891).

Health care self-efficacy was determined using three items adapted from the Stanford Patient Education Research Center Chronic Disease Self-Efficacy Scales.[23] These questions evaluate patients' confidence in asking

physicians about things that concern them, scheduling and attending doctor appointments when needing care, and receiving cancer-related follow-up care over the next 2 years. Responses comprised a 3-point Likert scale ranging from not at all confident to somewhat confident and totally confident. A summed score ranging from 0 to 6 was calculated, with higher scores indicating greater confidence in navigating the health care system for cancer-related care ($\alpha = .715$).

Cancer-related follow-up care. Participants were asked if they had attended cancer-related follow-up care in the previous 2 years.

Statistical Analysis

The prevalence of self-reported CRCI was determined for each cancer type and reported with the number of events and 95% CIs. We tested for significant differences in characteristics between subjects with CRCI and those without it using the Wilcoxon rank-sum test for continuous variables due to non-normality of data. For categorical variables, depending on the proportions of cells with counts of < 5, Pearson's chi-squared test ($< 20\%$) or Fisher's exact test ($\geq 20\%$) were used. Univariate and multivariate logistic (if outcome is rare, $\leq 15\%$) or log-binomial (if outcome is not rare, $> 15\%$) regression models were generated to determine the associations between self-reported CRCI and substance use. Adjusted confounders, including child at diagnosis (0-14 years), years since diagnosis, sex, race/ethnicity, cancer type, and cancer treatment intensity, were selected as these were socio-demographic variables and childhood cancer-related characteristics that remained unchanged before the presentation of the outcomes. Education and employment outcomes were then included in the model to verify the robustness of the findings with nonbaseline characteristics that had unclear temporal relationships with substance use.

Substance use behavior(s) that was significantly associated with CRCI was brought forward for mediation analysis conducted with the *paramed* package in Stata to determine the natural direct effect (NDE), natural indirect effect (NIE), and proportion mediated effect corresponding to each mediator.[24,25] NDE is defined as the average change in substance use behavior when CRCI is present as compared with when CRCI is absent while fixing the mediator to a level that naturally occurs in the absence of CRCI. NIE is defined as the average change in substance use behavior in the presence of CRCI, but the level of the mediator is changed from the level it would take if CRCI is absent to a level it would take if CRCI is present.[24,25] Determining NDE and NIE allows decomposition of the total effect (TE) of CRCI on substance use behaviors into direct and indirect components for a specific mediator.[26,27] For binary outcomes, TE would be equal to NDE $\times$ NIE. Hence, the proportion mediated effect is equal to $(\text{NDE} \times [\text{NIE} - 1])/(\text{TE} - 1) \times 100\%$, whereby TE is replaced by NDE $\times$ NIE.[26,27] Mediators of interest included attendance to a recent cancer-related follow-up care within the previous 2 years, number of late effects, and psychosocial variables (depressive symptoms, post-traumatic growth, and health care self-efficacy). These mediators were selected as these were actionable opportunities to manage substance use behaviors in both cancer and noncancer populations.[28-31] Each mediator was examined independent of other mediators. The same set of confounders was included for mediation analysis. Referring to Figure 1, we reasoned that this set of confounders were necessary to control for pathways A, B, and C to accurately quantify NDE and NIE. All statistical tests were two-sided, and $P < .05$ was considered statistically significant. As this was a secondary data analysis with a hypothesis-generating objective, adjustment for multiple testing was not conducted. Stata/SE version 16.1 was used to perform all analyses.

RESULTS

Factors Associated With CRCI

Of the 1,106 participants available for analysis, 144 (13%; 95% CI, 11 to 15%) reported problems with learning and memory. The highest prevalence of CRCI by cancer type (Data Supplement) was observed among brain/CNS cancer (25.4%) and leukemia (13.3%). A more detailed breakdown of cancer sites by self-reported CRCI can be found in the Data Supplement.

Participants self-reporting CRCI were younger at diagnosis, reported a lower education level, had public insurance, were more likely to be unemployed or disabled, and reported a larger number of cancer-related late effects than those without CRCI ($P < .05$; Table 1). Furthermore, those with CRCI reported more psychosocial problems

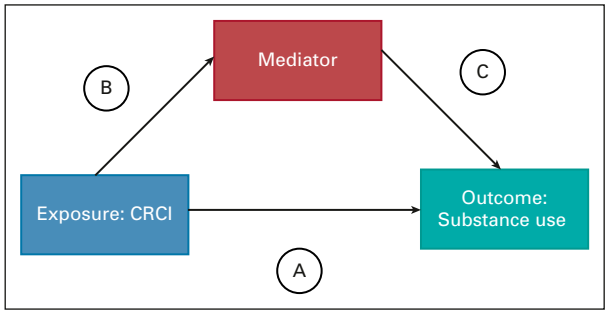

FIG 1. Direct acyclic graph with mediation. The direct acyclic graph illustrates the hypothesized simplified relationship between CRCI (exposure), substance use (outcome), and a mediator (attendance to a recent cancer-related follow-up care within the previous 2 years, number of late effects, depressive symptoms, post-traumatic growth, or health care self-efficacy). The direct pathway from the exposure to the outcome is represented by pathway A while the indirect pathway, though the mediator, is delineated by pathways B and C. CRCI, cancer-related cognitive impairment.

characterized by more depressive symptoms, less post-traumatic growth, and poorer health care self-efficacy, which may have influenced a higher attendance rate to a cancer-related follow-up care in the prior 2 years ($P < .05$; Table 1). After adjusting for potential confounders, self-reported CRCI was associated with having one more cancer-related late effect ($\beta = 1.34$; 95% CI, 1.17 to 1.51; $P < .001$; Data Supplement). Post hoc logistic regression analysis revealed that CRCI was associated with statistically higher odds of individual cancer-related late effects (Data Supplement).

CRCI and Current Substance Use

In the Project Forward Cohort (N = 1,106), the proportions of substance use behaviors included 32.0% for binge drinking (n = 354), 18.6% for marijuana use (n = 206), 11.4% for cigarette use (n = 126), 7.1% for e-cigarette/vaporizer use (n = 79), and 4.9% for prescription drug misuse (n = 54). Among participants with self-reported CRCI, there was a significantly larger proportion of current e-cigarette/vaporizer users (12.5% *v* 6.3%, $P = .023$) and fewer binge drinking participants (24.3% *v* 33.2%, $P = .021$) than among those without cognitive problems (Table 2). No significant difference was observed for cigarette, marijuana, and prescription drug misuse (Table 2). After confounder adjustment, self-reported CRCI was associated with 2.26 times the odds of current e-cigarette/vaporizer use (95% CI, 1.24 to 4.11; $P = .007$; Table 2), and this remains significant after including education and employment outcomes into the regression model (odds ratio, 2.42; 95% CI, 1.31 to 4.47; $P = .005$). As missingness was > 10% with current e-cigarette/vaporizer use, comparisons were made between those with (n = 986) and without (n = 120) e-cigarette/vaporizer use information. We found that certain characteristics differed, notably a higher proportion of participants with skin cancer (14.2% *v* 2.4%, $P < .001$) and lower prevalence of CRCI (3.3% *v* 14.2%, $P < .001$) among those who did not report vaping behavior (Data Supplement). Among the 120 participants with missing e-cigarette/vaporizer use information, 71 were not provided with the question during the initial study phase. Thus, sensitivity analysis excluding these 71 participants was conducted and showed that the CRCI and substance use associations were robust (data not reported). Considering these results, we proceeded with mediation analysis for e-cigarette/vaporizer use.

Mediation Analysis for CRCI and e-Cigarette/Vaporizer Use

Among the five mediators, on the basis of the NIE point estimates, 95% CIs, and *P* values, only depressive symptoms (CES-D) and number of late effects demonstrated a significant indirect pathway from CRCI to e-cigarette/vaporizer use (Data Supplement). The proportion mediated effect was the largest for late effects (82.6%), followed by depressive symptoms (48.5%), post-traumatic growth (22.5%), and health care self-efficacy (1.8%; Data Supplement). For recent cancer-related follow-up care, the proportion mediated effect could not be computed as this mediator has an opposing indirect effect on e-cigarette/vaporizer use when compared with CRCI, albeit without reaching statistical significance (Data Supplement).

DISCUSSION

Learning and memory problems were self-reported in one in eight YACCSs in the Project Forward Cohort, especially among survivors of brain/CNS cancer and leukemia, which is consistent with current literature.[1,4] Addressing our research question, self-reported CRCI was associated with higher odds of vaping and this relationship was significantly mediated by depressive symptoms and late effects. Those reporting CRCI had lower education levels, higher rates of unemployment and disabilities, poorer psychosocial outcomes, and more cancer-related late effects which are all characteristics understood of CRCI-afflicted YACCSs.[1,2,5] Our findings suggest that YACCSs face substantial challenges in coping with their cognitive and related complications as well as poor mental health, potentially leading to self-medication with vaping to improve concentration.

Information regarding vaping can be misleading or equivocal.[32] A common example of misinformation is the utility of vaping as a smoking cessation tool, which is opposed by existing smoking cessation guidelines.[32-34] The long-term health effects of vaping are also inconclusive due to recency of the phenomenon[32]; thus, there is need for prospective trials and cohort studies.[35] At least 23 chemicals, including nicotine, have been found in the liquid contents and emissions of vaping, and some were found to have carcinogenic effects.[35,36] There have also been multiple reports of vaping-associated acute lung injuries requiring hospitalization, intensive care, and mechanical intubation.[37] The available evidence is unable to substantiate claims of e-cigarette/vaporizers as being a safer alternative than tobacco and other substances in the short and long term, which should be emphasized to YACCSs.

Although we found poorer physical and mental health as mediators of CRCI-associated vaping, the reasons for vaping among YACCSs remain to be determined. Extrapolating from noncancer studies, e-cigarette/vaporizers have been used for stress management, smoking cessation/harm reduction (as a healthier substitute for combustible tobacco), and improving alertness and concentration, all of which are applicable to YACCSs, especially if they experience cognitive problems.[38,39] Surprisingly, attendance to cancer-related follow-up care did not significantly mediate the odds of CRCI-associated vaping. This could be explained with reference to Figure 1, which illustrates that the indirect pathway from CRCI to vaping can be broken down into pathways B (CRCI to cancer-related follow-up care) and C (cancer-related follow-up care to

TABLE 1. Characteristics of Participants by CRCI

Characteristic	Self-Reported CRCI			
	Yes (n = 144)	No (n = 962)	Total (N = 1,106)	*P*
Demographics				
Age, years, median (IQR)				
At diagnosis	11 (6-16)	13 (8-16)	13 (7-16)	.039*
At survey completion	25 (22-29)	26 (22-29)	25.5 (22-29)	.548
Years since diagnosis, median (IQR)	16 (11-19)	15 (11-18)	15 (11-18)	.033*
Sex, No. (%)				.976
Male	71 (49.3)	473 (49.2)	544 (49.2)	
Female	73 (50.7)	489 (50.8)	562 (50.8)	
Race/ethnicity, No. (%)				.354
Non-Hispanic White	42 (29.2)	282 (29.3)	324 (29.3)	
Hispanics	78 (54.2)	492 (51.1)	570 (51.5)	
Asians	10 (6.9)	97 (10.1)	107 (9.7)	
African American	10 (6.9)	43 (4.5)	53 (4.8)	
Others	4 (2.8)	48 (5.0)	52 (4.7)	
Highest education level, No. (%)				.020*
Less than high school	12 (8.3)	46 (4.8)	58 (5.2)	
High school graduate	31 (21.5)	174 (18.1)	205 (18.5)	
Some college	74 (51.4)	438 (45.5)	512 (46.3)	
College graduate	26 (18.1)	290 (30.1)	316 (28.6)	
Health insurance, No. (%)				.028*
Private	78 (54.2)	553 (57.5)	631 (57.1)	
Public	55 (38.2)	266 (27.7)	321 (29.0)	
Other	1 (0.7)	16 (1.7)	17 (1.5)	
Uninsured	7 (4.9)	95 (9.9)	102 (9.2)	
Employment, No. (%)				< .001***
Employed	56 (38.9)	531 (55.2)	587 (53.1)	
Unemployed or disabled	28 (19.4)	87 (9.0)	115 (10.4)	
Student	53 (36.8)	289 (30.0)	342 (30.9)	
SES, No. (%)				.637
First quintile (lowest)	31 (21.5)	216 (22.5)	247 (22.3)	
Second quintile	22 (15.3)	173 (18.0)	195 (17.6)	
Third quintile	21 (14.6)	168 (17.5)	189 (17.1)	
Fourth quintile	27 (18.8)	151 (15.7)	178 (16.1)	
Fifth quintile (highest)	23 (16.0)	155 (16.1)	178 (16.1)	
Missing	20 (13.9)	99 (10.3)	119 (10.8)	
Clinical characteristics				
Cancer type, No. (%)				< .001***
Skin	1 (0.7)	40 (4.2)	41 (3.7)	
Brain and other nervous system	43 (29.9)	126 (13.1)	169 (15.3)	
Endocrine	4 (2.8)	56 (5.8)	60 (5.4)	
Lymphoma	24 (16.7)	216 (22.5)	240 (21.7)	
Leukemia	52 (36.1)	340 (35.3)	392 (35.4)	
Others	20 (13.9)	184 (19.1)	204 (18.4)	

(continued on following page)

TABLE 1. Characteristics of Participants by CRCI (continued)

Characteristic	Self-Reported CRCI		Total (N = 1,106)	P
	Yes (n = 144)	No (n = 962)		
Treatment intensity, No. (%)				.244
1 (least intensive)	7 (4.9)	74 (7.7)	81 (7.3)	
2	51 (35.4)	361 (37.5)	412 (37.3)	
3	73 (50.7)	474 (49.3)	547 (49.5)	
4 (most intensive)	13 (9.0)	53 (5.5)	66 (6.0)	
No. of late effects,[a] median (IQR)	1.5 (1-3)	0 (0-1)	0 (0-1)	< .001***
Cancer-related follow-up care				
Attended a cancer-related follow-up care within prior 2 years, No. (%)	92 (63.9)	540 (56.1)	632 (57.1)	.030*
Psychosocial outcomes				
CES-D,[b] median (IQR)	18 (11-28)	10 (5-19)	11 (6-20)	< .001***
Modified Post-Traumatic Growth Inventory,[c] median (IQR)	3.61 (3.00-4.28)	3.89 (3.44-4.39)	3.83 (3.39-4.33)	< .001***
Health care self-efficacy,[d] median (IQR)	5 (4-6)	5 (4-6)	5 (4-6)	.033*

Abbreviations: CES-D, Center for Epidemiological Studies Depression Scale; CRCI, cancer-related cognitive impairment; IQR, interquartile range; SES, socioeconomic status.

[a]Late effects include inability to have children, heart problems, second cancer, weight gain, liver damage, lung problems, poor eyesight, sexual functioning problems, and bone fractures.

[b]The CES-D measures the level of depressive symptoms. Higher sum scores represent a greater level of symptoms.

[c]Higher scores indicate higher post-traumatic growth.

[d]Higher scores represent greater health care self-efficacy.

*$P < .05$. **$P < .01$. ***$P < .001$.

vaping). Reduced associations at either pathway would contribute to the lack of significant indirect effect. In the Project Forward Cohort, 40% of the YACCSs suffered from CRCI did not attend cancer-related follow-up care and reasons for their nonattendance should be further explored. Dropping out of care often occurs during the phase of adulthood transition, which is marked by major changes in life, responsibilities, and stressors across education, employment, leaving home, marriage, and parenthood.[40] Unstructured transitional care from pediatric to adult-centric clinics and inadequate psychosocial support encompassing information needs regarding health insurance, anxiety, stress coping, and financial toxicity discouraged YACCSs from engaging long-term follow-ups.[41,42] For pathway C, we speculate that vaping behavior may not be asked specifically during the visits but more generally as substance misuse in clinical setting. Moreover, vaping as a substance misuse behavior remains contentious, not forgetting that young

TABLE 2. Association of CRCI and Current Substance Use

Outcome	Self-Reported CRCI, No. (%)		P[a]	Crude (95% CI)	P[b]	Adjusted[c] (95% CI)	P[b]
	Yes (n = 144)	No (n = 962), Ref Group					
Logistic regression (OR)							
Cigarette use (n = 1,086)	21 (14.6)	105 (10.9)	.230	1.36 (0.82 to 2.26)	.232	1.43 (0.84 to 2.44)	.190
Prescription drug misuse (n = 1,090)	4 (2.8)	50 (5.2)	.196	0.51 (0.18 to 1.44)	.204	0.53 (0.18 to 1.50)	.229
e-cigarette/vaporizer use (n = 986)	18 (12.5)	61 (6.3)	.023*	1.90 (1.09 to 3.32)	.025*	2.26 (1.24 to 4.11)	.007**
Log-binomial regression (risk ratio)							
Binge drinking (n = 1,083)	35 (24.3)	319 (33.2)	.021*	0.72 (0.53 to 0.96)	.030*	0.76 (0.56 to 1.03)	.079
Marijuana use (n = 1,083)	29 (20.1)	177 (18.4)	.714	1.07 (0.75 to 1.52)	.712	1.11 (0.78 to 1.59)	.562

Abbreviations: CRCI, cancer-related cognitive impairment; OR, odds ratio; ref, reference.

[a]*P* values for Pearson's chi-squared test.

[b]*P* values for logistic/log-binomial regression.

[c]The multivariate models were adjusted for child at diagnosis (0-14 years), years since diagnosis, sex, race/ethnicity, cancer type, and treatment intensity.

*$P < .05$. **$P < .01$.

patients with cancer do not feel the need to discuss their substance use behavior with their providers.[43] Possible strategies to enhance the effectiveness of follow-up care to reduce vaping behaviors include individualized health educational programs, peer navigators, and mobile health (mHealth) applications to increase follow-up rates,[44-46] intervening on physical and mental health issues of these YACCSs as observed in our mediation analysis findings, and following up on vaping-related behaviors during the visits. Nevertheless, research is needed to fully understand the motivations behind the uptake of vaping in YACCSs.

The current study is limited by its study design as a secondary data analysis of a cross-sectional data set. The question for determining CRCI status in the study was brief compared with the gold standard of using a robust psychometric tool (eg, PROMIS Cognitive Function Short Form 8a or Functional Assessment of Cancer Therapy—Cognitive Function) together with neuropsychological cognitive batteries,[47,48] although our findings on CRCI prevalence and correlates agreed with current literature[1-5] and provided confidence in this classification approach. Anxiety, a key mediator of substance use, was not assessed in the original cohort.[49] Our questions regarding substance use behaviors are also less detailed compared with other substance use questionnaires such as the National Survey of Drug Use and Health[50] and the National Epidemiologic Survey on Alcohol and Related Conditions.[51] For instance, prescription drug misuse could be further subdivided by its indications (pain relief, stimulant, or depressant), and female binge drinking behavior should have been defined as 4+ drinks in a single occasion instead of 5+ drinks.[50] This may have led to nondifferential misclassification of substance use behaviors with bias to the null for cigarette use, binge drinking, prescription drug misuse, and marijuana use. Data regarding other behaviors of clinical significance, such as misuses of illicit drugs, were not explored as they were not asked to the participants. We recommend that researchers continue to explore the relationship between substance use behaviors and CRCI and not limiting to only vaping, in future studies. Due to the cross-sectional design, causal inference cannot be established. The high proportion of missing e-cigarette/vaporizer use data further limited the interpretability of the results. Additionally, because the racial and ethnic composition in Los Angeles county is different from the demographic breakdown of YACCSs in the United States,[52] our prevalence of substance use behaviors may not be applicable in other states and countries. However, our observed associations between CRCI and vaping are likely applicable in other U.S. states as race/ethnicity were controlled for in the analysis, but we would encourage research to be conducted in other states and countries to account for state- and country-level differences in legality and societal standards. Nonetheless, the association between CRCI and vaping has not been previously investigated. This paper serves as preliminary evidence for future vaping-associated studies in YACCSs and highlights the importance of such studies to better educate the benefits and risks of vaping to young cancer survivors.

In conclusion, we have demonstrated preliminary evidence that there are higher odds of vaping among patients with self-reported CRCI in a cohort of YACCSs. Cancer-related follow-up visits present opportunities for oncologists and other clinicians to correct misconceptions and address physical and mental health issues that may facilitate the uptake of vaping behavior. Interventions that encourage engagement in long-term cancer-related follow-up care visits through a survivor-focused care model that targets unmet health and psychosocial needs of survivors will also help with reducing vaping and other substance use behaviors. Future research is needed to confirm our findings with longitudinal studies, investigate reasons for vaping among YACCSs, determine the long-term health effects of vaping, evaluate the relationship between CRCI and substance use behaviors (other than vaping) with detailed measures, and develop new interventions or validate existing ones to increase cancer-related follow-up rates.

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