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Cigarette smoking and pulmonary function in adult survivors of childhood cancer exposed to pulmonary-toxic therapy: Results from the St. Jude Lifetime Cohort Study

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Abstract

Treatments for childhood cancer can impair pulmonary function. We assessed the potential impact of cigarette smoking on pulmonary function in 433 adult childhood cancer survivors (CCS) who received pulmonary-toxic therapy, using single breath diffusion capacity for carbon monoxide corrected for hemoglobin (DLCO_{corr}), forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), and total lung capacity (TLC). FEV₁/FVC median values among current (1.00; interquartile range (IQR): 0.94–1.04) and former smokers (0.98; IQR: 0.93–1.04) were lower than those who had never smoked (1.02; IQR: 0.96–1.06) ($p = 0.003$). Median FEV₁/FVC values were lower among those who smoked ≥ 6 pack-years (0.99; IQR: 0.92–1.03) and those who smoked < 6 pack-years (1.00; IQR: 0.94–1.04), than among those who had never smoked ($p=0.005$). Our findings suggest that CCS have an increased risk for future obstructive and restrictive lung disease. Follow-up is needed to determine if smoking imparts more than additive risk. Smoking prevention and cessation need to be a priority in this population.

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Keywords

Addictive substances/nicotine; Epidemiology of survivorship; Long-term toxicities

Introduction

Five-year survival for childhood cancer increased from less than 50% before 1970 to 83% in 2009 [1], resulting in greater attention to adverse late outcomes among the more than 420,000 survivors estimated to be in the US [2]. Childhood cancer survivors (CCS) have increased mortality from pulmonary complications [3]. Among those exposed to pulmonary-toxic cancer treatment, 65.2% reportedly have abnormal pulmonary function [4].

We hypothesize that cigarette smoking, a well-established risk factor for pulmonary disease [5], may exacerbate pulmonary impairment among CCS exposed to pulmonary-toxic therapy. While adult CCS have lower rates of cigarette smoking than the general population [5, 6] and those of healthy control subjects [7, 8], one-third report having initiated smoking during their lifetime, one-fifth continue to smoke [6], and they may be less likely than non-cancer survivors to quit smoking [9].

The impact of smoking on pulmonary function among CCS at risk for therapy-related pulmonary dysfunction has not been well assessed. We undertook the present analysis to determine if an adverse effect of smoking is already apparent in a young cohort of CCS.

Materials and Methods

Participants were identified from the IRB approved St. Jude Lifetime Cohort Study (SJLIFE) [10, 11], comprised of individuals treated for a childhood malignancy at St. Jude Children's Research Hospital who are >10 years from diagnosis and aged >18 years.

Risk-based assessment of pulmonary function was performed according to the Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancer if their cancer treatment included pulmonary lobectomy, pulmonary metastasectomy or pulmonary wedge resection, bleomycin, busulfan, lomustine (BCNU) or carmustine (CCNU), or radiation therapy treatment to the chest (thorax), whole lung, mediastinum, axilla, mini-mantle, mantle, extended mantle, total lymphoid irradiation, subtotal lymphoid irradiation, or total body irradiation [12]. Surgical procedures, cumulative doses for chemotherapeutic agents, and radiation treatment fields, dose, and energy source were obtained from medical records by trained abstractors using standard methods [10].

Spirometry was used to measure forced vital capacity (FVC) [13], forced expiratory volume in 1 second (FEV_1) [13], and single breath diffusion capacity for carbon monoxide corrected for hemoglobin ($DLCO_{corr}$) [14]. Total lung capacity (TLC) [15] was determined by body plethysmography. All tests were performed according to the American Thoracic Society standard [16, 17]. Results are expressed as percent of predicted using race-, age-, and sex-appropriate equations. Obstructive lung disease ($FEV_1/FVC < 0.70$) was evaluated using the GOLD criteria [18]. Restrictive lung disease ($TLC < 75\%$ predicted) was evaluated using the

Guide to the Evaluation of Permanent Impairment [19]. Participants reporting having smoked more than 100 cigarettes in their life were considered smokers [20], and pack-years of tobacco use were calculated from self-reported smoking history [6].

The null hypotheses of equal distributions of pulmonary measures between current, former, and never-smokers, as well as between smokers smoking ≥ 6 pack-years, < 6 pack-years, and never-smokers were tested using the Kruskal-Wallis (KW) test. Pairwise comparisons between these groups were performed using the Dwass, Steel, Critchlow-Flinger multiple comparison procedure (DSCF). Associations for categorical variables were compared using χ^2 tests or Exact χ^2 tests. All tests were two-tailed with $\alpha=0.05$. SAS v9.3 (SAS Institute Inc., Cary, NC) was used for all analyses.

Results

At the time of this analysis, 433 of 719 SJLIFE participants (60.2%) who fulfilled the eligibility for pulmonary evaluation had completed pulmonary function testing (Supplemental Figure 1 and Supplemental Table 1). The median age of our study population was 35 years (Interquartile Range (IQR): 30–41). The median time since diagnosis was 23 years (IQR: 18–29). With the exception of race/ethnicity, demographic and therapy-related exposure factors did not differ according to smoking status (Table 1).

Current smokers had smoked a median of 8.1 pack-years (IQR: 3.1–16.5). Former smokers had smoked a median of 4.5 pack-years (IQR: 1.5–9.6), and quit smoking a median of 10.0 years (IQR: 5.0–16.0) prior to assessment of pulmonary function.

The distributions of FEV₁/FVC for current, former and never smokers were different [$p = 0.003$ (KW)] (Figure 1A), with poorer pulmonary function on average for current and former smokers. FEV₁/FVC values were progressively worse for survivors who smoked < 6 pack-years and ≥ 6 pack-years compared with survivors who never smoked [$p = 0.005$ (KW)] (Figure 1B). Current smokers had lower median DLCO_{corr} compared with former smokers and non-smokers (Table 2) and the DLCO_{corr} distribution between current, former and never smokers was different [$p = 0.017$ (KW)]. The distributions of TLC did not differ statistically by smoking status [$p = 0.11$ (KW)]. Analyses restricted to the 282 survivors with pulmonary radiation but not pulmonary toxic chemotherapy, provided essentially identical median values (Supplementary Table 2).

Only one former smoker and one individual who had never smoked met the criterion for diagnosis of obstructive lung disease (FEV₁/FVC < 0.70). By contrast, restrictive lung disease (TLC $< 75\%$) was present in 25.3% of current smokers, 30.4% of former smokers and 34.6% of those who had never smoked, although random variability may explain the differences by smoking status [$p = 0.27$ (χ^2)].

Discussion

Given the established association between cigarette smoking and impaired pulmonary function in the general population [21], one might expect a negative impact of smoking among CCS, particularly those who have sustained exposures to pulmonary-toxic cancer

treatments. We present empirical data documenting the occurrence of impaired pulmonary function among CCS who smoke. Our findings are particularly important given the young age of the study population (i.e., median of 35 years, with 50% being between the ages of 30 and 41) and low cumulative exposure to cigarettes (with a median of only 6.4 pack-years).

Pulmonary function among non-smokers naturally declines with increasing age[13].

The magnitude of functional impairment is correlated with the total pack-years of cigarette smoking, is apparent in non-cancer populations after as few as ten pack-years, and is characterized by declines in FEV₁, consistent with obstructive pulmonary disease [22]. Participants in the Lung Health Study demonstrated continued deterioration of their pulmonary function during the course of the study, with follow-up extended as long as eleven years after initial study enrolment. Among those randomized in the Lung Health Study to usual care who continued to smoke, FEV₁ % predicted decreased 1.44%/year, compared to 1.02%/year among intermittent smoking quitters and 0.40%/year among permanent smoking quitters. This suggests that, in this population of middle aged (35 to 60 years at study entry) cigarette smokers, those who smoked intermittently during the course of the study resembled those who continued to smoke continuously more closely than those who had quit smoking [23], a finding that is consistent with our results of a dose-response relationship between DLCO_{corr} and FEV₁/FVC and pack-years.

We identified a negative impact of smoking in a young population with modest smoking exposure. These survivors may be at risk of accelerated progression of serious pulmonary morbidity and mortality. For example, CCS at risk for treatment-related adverse cardiac outcomes experience a greater than additive risk from modifiable cardiac risk factors such as hypertension, obesity, and dyslipidemia [24], a scenario that is possible for adverse pulmonary outcomes and interaction between pulmonary-toxic therapy and smoking.

The present study has several limitations. Smoking history was ascertained by participant self-report. The accuracy of self-reported smoking varies not only by study population but also by the gold standard used for comparison (e.g. saliva or urine cotinine) [25]. Unfortunately, the accuracy of self-reported smoking among adult CCS is unknown, and we lacked a gold standard measurement for comparison. In addition, we did not have a concurrent control group. However, there are widely accepted age-, sex- and race- specific normative values for PFTs in the US population, which we utilized to calculate our pulmonary outcomes, expressed as the percent of predicted. Thus, the results we report are adjusted to a normative population.

Regardless of the magnitude of the future risk, our data reinforce the urgency of applying known effective approaches for smoking cessation to the estimated 17–23% of CCS who smoke [6]. Of greater importance is the need to integrate programs for effective smoking prevention [5] into the care of newly diagnosed pediatric cancer patients as well as the ongoing care and follow-up of CCS. Furthermore, continued follow-up and evaluation of this high-risk population will provide insights into the level of risk smoking imparts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

FEV₁/FVC distribution for survivors at risk of pulmonary impairment based upon childhood cancer treatment, by current smoking status (Panel A), by pack-years of tobacco smoking (Panel B)

Table 1

Frequencies of demographic and treatment variables among current, former and non-smokers who underwent pulmonary function testing

Variable	Total (N=433)	Current smoker (N=84)	Former smoker (N=80)	Never smoker (N=269)	p-value*
Sex					
Male	212	50.0%	55.0%	46.8%	0.43
Female	221	50.0%	45.0%	53.2%	
Race					
Non-Hispanic White	363	85.7%	96.3%	79.6%	0.02
Non-Hispanic Black	58	13.1%	2.5%	16.7%	
Hispanic	8	0.0%	1.2%	2.6%	
Other	4	1.2%	0.0%	1.1%	
Age at diagnosis (years)					
0 to 4	60	15.5%	10.0%	14.5%	0.94
5 to 9	88	21.4%	20.0%	20.1%	
10 to 14	139	31.0%	36.3%	31.2%	
15 to 22	146	32.1%	33.7%	34.2%	
Age at evaluation (years)					
19 to 25	49	11.9%	8.8%	11.9%	0.10
26 to 35	172	36.9%	32.5%	42.7%	
36 to 45	161	34.5%	40.0%	37.2%	
46 to 58	51	16.7%	18.7%	8.2%	
Bleomycin					
No	338	78.6%	83.8%	76.2%	0.36
Yes	95	21.4%	16.2%	23.8%	
Busulfan					
No	422	96.4%	97.5%	97.8%	0.91
Yes	11	3.6%	2.5%	2.2%	
Carmustine					
No	426	97.6%	100.0%	98.1%	0.58

Variable	Total (N=433)	Current smoker (N=84)	Former smoker (N=80)	Never smoker (N=269)	p-value*
Yes	7	2.4%	0.0%	1.9%	
Lomustine					
No	424	97.6%	96.3%	98.5%	0.45
Yes	9	2.4%	3.7%	1.5%	
Chest radiation therapy					
No	84	21.4%	16.2%	19.7%	0.69
Yes	349	78.6%	83.8%	80.3%	
Lung surgery					
No	359	84.5%	80.0%	83.3%	0.72
Yes	74	15.5%	20.0%	16.7%	
Chest RT only**					
No	151	36.9%	31.2%	35.3%	0.73
Yes	282	63.1%	68.8%	64.7%	
Chemotherapy only**					
No	379	86.9%	92.5%	86.3%	0.34
Yes	54	13.1%	7.5%	13.7%	
Chest RT + Chemotherapy**					
No	366	84.5%	85.0%	84.4%	0.99
Yes	67	15.5%	15.0%	15.6%	

* χ^2 or exact χ^2 test

** +/- lung surgery

Table 2

Pulmonary function among adult survivors of childhood cancer.

Pulmonary Function Study and Smoking Characteristics	N	% Predicted		P-value ^a
		Median	IQR	
TLC (Pleth)	428 ^b	82.0	70.0 to 92.5	
Never smoker	266	80.0	69.0 to 91.0	
Former smoker	79	82.0	73.0 to 93.0	0.54
Current smoker	83	87.0	74.0 to 94.0	0.12
Ever Smoker < 6 PY	67	81.0	70.0 to 90.0	0.98
Ever Smoker ≥ 6 PY	80	86.5	74.0 to 94.0	0.08
DLCO_{corr}	429 ^c	77.0	65.0 to 87.0	
Never smoker	266	77.5	66.0 to 89.0	
Former smoker	80	77.0	68.5 to 86.5	0.99
Current smoker	83	74.0	60.0 to 82.0	0.02
Ever Smoker <6 PY	68	77.5	64.5 to 85.0	0.96
Ever Smoker ≥ 6 PY	80	71.5	62.0 to 81.0	0.03
FEV₁/FVC	433	1.00	0.95 to 1.05	
Never smoker	269	1.02	0.96 to 1.06	
Former smoker	80	0.98	0.93 to 1.04	0.01
Current smoker	84	1.00	0.94 to 1.04	0.03
Ever Smoker <6 PY	69	1.00	0.94 to 1.04	0.38
Ever Smoker ≥ 6 PY	80	0.99	0.92 to 1.03	0.005
FEV₁	433	78.0	67.0 to 90.0	
Never smoker	269	79.0	69.0 to 92.0	
Former smoker	80	76.5	65.5 to 86.0	0.23
Current smoker	84	79.5	67.0 to 89.0	0.83
Ever Smoker <6 PY	69	79.0	69.0 to 88.0	0.66
Ever Smoker ≥ 6 PY	80	78.0	66.0 to 87.0	0.38
FVC	433	80.0	67.0 to 91.0	
Never smoker	269	79.0	67.0 to 91.0	
Former smoker	80	77.0	67.5 to 88.0	0.80
Current smoker	84	83.0	70.0 to 90.0	0.88
Ever Smoker <6 PY	69	80.0	68.0 to 87.0	0.85
Ever Smoker ≥ 6 PY	80	81.5	68.0 to 88.5	0.99

FVC - Forced Vital Capacity; FEV₁ - Forced Expiratory Volume In 1 Second; DLCO_{corr} - Single Breath Diffusion Capacity for Carbon Monoxide Corrected for Hemoglobin; TLC - Total Lung Capacity; PY - Pack-Years; N - Number of participants; IQR - Interquartile Range;

^a Comparison is to Never smokers, using the Dwass, Steel, Critchlow-Flinger procedure;

^b Five subjects were not evaluable for TLC;

^c Four subjects were not evaluable for DLCO_{corr}