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ORIGINAL REPORT

Long-Term Pulmonary Function in Survivors of Childhood Cancer

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ABSTRACT

Purpose
This study was undertaken to determine the magnitude of pulmonary dysfunction in childhood cancer survivors when compared with healthy controls and the extent (and predictors) of decline over time.

Patients and Methods
Survivors underwent baseline (t1) pulmonary function tests, followed by a second comprehensive evaluation (t2) after a median of 5 years (range, 1.0 to 10.3 years). Survivors were also compared with age- and sex-matched healthy controls at t2.

Results
Median age at cancer diagnosis was 16.5 years (range, 0.2 to 21.9 years), and time from diagnosis to t2 was 17.1 years (range, 6.3 to 40.1 years). Compared with odds for healthy controls, the odds of restrictive defects were increased 6.5-fold (odds ratio [OR], 6.5; 95% CI, 1.5 to 28.4; $P < .01$), and the odds of diffusion abnormalities were increased 5.2-fold (OR, 5.2; 95% CI, 1.8 to 15.5; $P < .01$). Among survivors, age younger than 16 years at diagnosis (OR, 3.0; 95% CI, 1.2 to 7.8; $P = .02$) and exposure to more than 20 Gy chest radiation (OR, 5.6; 95% CI, 1.5 to 21.0; $P = .02$, referent, no chest radiation) were associated with restrictive defects. Female sex (OR, 3.9; 95% CI, 1.7 to 9.5; $P < .01$) and chest radiation dose (referent: no chest radiation; ≤ 20 Gy: OR, 6.4; 95% CI, 1.7 to 24.4; $P < .01$; > 20 Gy: OR, 11.3; 95% CI, 2.6 to 49.5; $P < .01$) were associated with diffusion abnormalities. Among survivors with normal pulmonary function tests at t1, females and survivors treated with more than 20 Gy chest radiation demonstrated decline in diffusion function over time.

Conclusion
Childhood cancer survivors exposed to pulmonary-toxic therapy are significantly more likely to have restrictive and diffusion defects when compared with healthy controls. Diffusion capacity declines with time after exposure to pulmonary-toxic therapy, particularly among females and survivors treated with high-dose chest radiation. These individuals could benefit from subsequent monitoring.

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INTRODUCTION

Childhood cancer survivors are at risk for late-occurring pulmonary complications resulting from therapeutic exposures such as lung irradiation, pulmonary-toxic chemotherapy, lung surgery, or as a result of hematopoietic cell transplantation (HCT) –associated chronic graft-versus-host disease (cGVHD).[1,2] Five-year survivors have a nearly nine-fold excess risk of dying as a result of pulmonary compromise when compared with age- and sex-matched individuals without a history of cancer[3]; the cumulative incidence of pulmonary disease increases with time from diagnosis,[4,5] suggesting that childhood cancer survivors increasingly face pulmonary morbidity as they age.

The prevalence of pulmonary dysfunction reported in previous cross-sectional studies ranges from 20% to 100%.[2] The wide range can be attributed to small, convenience samples and the use of various definitions of pulmonary dysfunction.[2,6-8] Prospective studies have focused on the early (< 5 years from diagnosis) period,[2] providing us with little information regarding long-term changes in pulmonary function in survivors. Few studies have included age- and sex-matched noncancer controls,[9,10] and none have examined the impact of abnormal lung function on health-related quality of life

(HRQOL) or the role of blood biomarkers of lung injury[11,12] (transforming growth factor beta1 [TGF-β1], platelet-derived growth factor A/B [PDGF-A/B], surfactant proteins A and D[SP-A/D]) in screening for pulmonary dysfunction long after completion of cancer therapy.

The Children's Oncology Group (COG) Long-Term Follow-Up (LTFU) Guidelines[1,13] recommend that survivors exposed to pulmonary-toxic therapy undergo a one-time pulmonary function testing (PFT) and symptom assessment at the time of transition into LTFU care, with subsequent testing as clinically indicated. However, a paucity of information regarding the trajectory of change in pulmonary function with time has precluded the development of guidelines regarding the frequency and duration of subsequent screenings. This study addresses these gaps in knowledge by using both cross-sectional and longitudinal study designs to examine long-term pulmonary outcomes in childhood cancer survivors.

PATIENTS AND METHODS

Study participants were recruited from the Childhood Cancer Survivorship Clinic at City of Hope (COH); clinic eligibility criteria included cancer diagnosed at younger than age 22 years and $\geq$ 2 years since completion of cancer treatment. As previously described,[6] all participants in this clinic undergo risk-based screening by using a research protocol that adheres to the recommendations of the COG LTFU Guidelines. Criteria for PFT screening are as follows: (1) previous exposure to pulmonary-toxic chemotherapy (bleomycin, busulfan, nitrosoureas), and/or (2) chest radiation (Data Supplement), and/or (3) history of allogeneic HCT with cGVHD, and/or (4) pulmonary surgery (lobectomy, metastectomy, or wedge resection).

One hundred fifty-five individuals had undergone a baseline (t1) PFT at entry into the COH Survivorship Clinic (median time from diagnosis, 12.2 years; range, 4.3 to 36.5 years). Among the 155 survivors who had undergone baseline (t1) PFTs, two (1.3%) died (one as a result of a second malignant neoplasm and one as a result of relapse), and four (2.6%) had relapsed or developed an second malignant neoplasm but were alive, leaving 149 individuals who were eligible for a second pulmonary function assessment (t2; Appendix Fig A1, online only). Of these 149 survivors, 25 (16.8%) were lost to follow-up, and two (1.3%) refused participation. This article includes results from the 121 survivors (81.2%) who completed both a baseline (t1) and follow-up evaluation (t2) at a median of 5.0 years (range, 1.0 to 10.3 years) from t1.

There were no statistically significant demographic or treatment-related differences between cancer survivors who underwent a PFT at t2 (n = 121) and those who did not (n = 34; Appendix Table A1, online only). Importantly, there were no differences in the prevalence of baseline lung function abnormalities between the two groups.

Healthy controls with no history of cancer or pulmonary disease were recruited at t2 from the general population, frequency-matched on sex and age at participation (Data Supplement). The study was approved by the COH institutional review board. All study participants and/or their parents or legal guardians provided written informed consent.

Pulmonary Function Evaluation

Study participants underwent a detailed physical examination, with special attention to signs and symptoms of pulmonary dysfunction, and completed a modified five-item Medical Research Council Dyspnea Questionnaire[14] (Data Supplement). Individuals were considered to have symptomatic pulmonary disease if they answered "yes" to two or more of the Medical Research Council Dyspnea Questionnaire items. PFTs were performed on the day of clinical evaluation according to the American Thoracic Society recommendations[15,16] and included total lung capacity (TLC), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), FEV_1/FVC ratio, diffusing capacity of the lungs for carbon monoxide (DL_{CO}), and DL_{CO}/volume of air (DL_{CO}/V_A). Percent of predicted normal values were calculated by using established reference values. If DL_{CO} was less than 80% of the predicted value, then DL_{CO} corrected for hemoglobin content (DL_{COcorr}), age, and sex was calculated.[17] All PFTs were interpreted by the study pulmonologist (D.H.) who was blinded to the status of the study participants.

Blood Biomarkers

Blood samples collected on the day of clinical assessment were used to measure TGF-β1 and PDGF-A/B (Luminex xMAP Technology Kit, Millipore, St. Charles, MO; lower limit of detection: TGF-β1, 6.0 pg/mL; PDGF-A, 0.4 pg/mL; PDGF-B, 2.2 pg/mL) and SP-A and SP-D (Surfactant Protein ELISA, MyBioSource, San Diego, CA; range, 0.5 to 60 ng/mL and 7.8 to 500 ng/mL, respectively).

Clinical Data Collection

Demographics and health behaviors. Self-reported questionnaires completed by survivors and controls were used to obtain data on demographics, insurance, physical activity, smoking history, and history of cardiomyopathy/heart failure.[18]

HRQOL. Study participants (survivors and controls) who were age 18 years or older at study participation (94.5% of all participants) completed the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36).

Clinical information. Medical records (survivors only) provided the date of diagnosis; type of cancer; history of cardiomyopathy and/or heart failure; cGVHD; cumulative exposure to bleomycin, busulfan, and nitrosoureas; and receipt of and total prescribed dose of chest-directed (Data Supplement) radiation and surgery.

Statistical Analysis

Cancer survivors and controls were compared at t2. The primary outcome was pulmonary dysfunction, as defined by moderate-to-severe obstructive lung disease (FEV_1/FVC $<$ 0.7 and FEV_1 $<$ 80% of predicted [Global Initiative for Chronic Obstructive Lung Disease; GOLD[19] criteria]), restrictive lung disease (TLC $<$ 75% and FEV_1 $\geq$ 80% predicted [grade $\geq$ 2 according to Common Terminology Criteria for Adverse Events v3.0; CTCAE v3.0][20]), or diffusion capacity abnormality (DL_{COcorr} $<$ 75% predicted [grade $\geq$ 2 per CTCAE v3.0]). The prevalence of obstructive disease, restrictive disease, and diffusion abnormalities among the survivors exposed to pulmonary-toxic therapy was projected to be 3%, 20%, and 35%, respectively[8]; the expected prevalence in controls was estimated to be 1%, 2%, and 4%, respectively.[21-23] Assuming a type I error of 0.017 (accounting for multiple testing), enrolling approximately 120 childhood cancer survivors and 40 healthy controls provided more than 80% power to detect a significant difference in the prevalence of defects between cancer survivors and controls.

Descriptive statistics for pulmonary function indices and blood biomarkers were generated for cancer survivors and controls. Among cancer survivors, pulmonary function indices were compared by therapeutic exposures and clinical characteristics. Categorical variables were compared by using χ^2 tests. Mean domain-specific scores were compared by using independent two-sample *t* tests or analysis of variance. Pearson's correlation was calculated between continuous variables (pulmonary function indices and blood biomarkers).

Predictors of Pulmonary Disease at t2

Dependent variables included restrictive lung disease and diffusion capacity abnormality. The low prevalence of obstructive lung disease precluded further analysis.

Survivors versus controls. Independent variables assessed were age at examination ($<$ 30/$\geq$ 30 years old), sex, race/ethnicity (non-Hispanic white, Hispanic, other), health insurance at evaluation (yes/no), exercise ($<$ 3/$\geq$ 3 days per week), body mass index at examination ($<$ 25/$\geq$ 25 kg/m^2), smoking history (ever, never), and cardiomyopathy and/or heart failure at the time of evaluation (yes/no).

Within childhood cancer survivors analyses. Additional independent variables assessed included diagnosis (lymphoma, leukemia, solid malignancy), age at cancer diagnosis ($<$ 16/$\geq$ 16 years old), time since diagnosis

Table 1. Patient and Treatment Characteristics

Characteristic	Survivors (n = 121) No.	%	Controls* (n = 43) No.	%	P
Male sex	61	50.4	23	53.4	.73
Age at examination, years					.80
Median	32.3		33.5		
Range	14.6-58.9		14.8-56.9		
Race/ethnicity					
Non-Hispanic white	45	37.2	22	51.2	
Hispanic	59	48.8	9	20.9	
Other	17	14.0	12	27.9	< .01
Body mass index ≥ 25 at examination	55	45.5	19	44.2	.89
Currently employed part-time or full-time	81	68.1	35	81.4	.10
Currently insured	87	71.9	40	93.0	< .01
Exercise ≥ 3 days per week	71	58.7	22	51.2	.39
Minutes per week of exercise					.30
Median	150		120		
Range	0-840		0-1,260		
Ever-smoker	6	5.0	5	11.6	.13
Cardiomyopathy	8	6.6	0		.09
Diagnosis					
Lymphoma	48	39.7	—		—
Hodgkin	41	33.9	—		—
Non-Hodgkin	7	5.8	—		—
Leukemia	43	35.5	—		—
Acute lymphoblastic	20	16.5	—		—
Acute myeloid	17	14.0	—		—
Other	6	5.0			
Solid malignancy	30	24.8	—		—
Sarcoma	13	10.7	—		—
Other	17	14.1	—		—
Age at diagnosis, years					
Median	16.5		—		—
Range	0.2-21.9				
Time since diagnosis, years					
Median	17.1		—		—
Range	6.3-40.1				
Treatment details					
Cumulative dose of bleomycin, IU/m^2					
Median	60		—		—
Range	30-360				
Any	42	34.7	—		—
Cumulative dose of busulfan, mg/m^2					
Median	436		—		—
Range	115-1,102				
Any	15	12.4	—		—
Cumulative dose of BCNU or CCNU, mg/m^2					
Median	450		—		—
Range	225-987				
Any	12	9.9	—		—
Chest radiation therapy, Gy					
Median	13.2		—		—
Range	2-76				
None	32	26.4	—		—
≤ 20 Gy	60	49.6	—		—
> 20 Gy	29	24.0	—		—
Surgery (any)			—		—
Lobectomy, wedge resection, metastectomy	7	5.8	—		—
Hematopoietic cell transplantation					
None	57	47.1	—		—
Autologous	20	16.5	—		—
Allogeneic	44	36.4	—		—
Overall treatment			—		—
Chemotherapy only	31	25.6	—		—
Radiation therapy only	32	26.4	—		—
Chemotherapy + radiation therapy	58	48.0	—		—

Abbreviations: BCNU, carmustine; CCNU, chloroethylcyclohexylnitrosourea.
*Frequency-matched to cancer survivors by sex and age at participation.

(< 17/≥ 17 years), bleomycin (none, any), busulfan (none, any), nitrosoureas (none, any), chest radiation (none, ≤ 20 Gy, > 20 Gy), and HCT (none, autologous, allogeneic).

Variables included in the multivariable logistic regression analysis were those associated ($P < .2$) with the dependent variable in the univariable analysis. Data were analyzed by using SPSS Version 18.0 (IBM, Armonk, NY). All statistical tests were two-sided, and $P < .05$ was considered statistically significant.

Predictors of Change in Pulmonary Function Over Time (t1 to t2)

Multivariable regression analysis was used to identify variables associated with progressive diffusion abnormality (decline in function between t1 and t2) in survivors with normal function at baseline. The low prevalence of progressive obstructive or restrictive lung disease in individuals with normal function at baseline precluded similar analyses for these outcomes.

RESULTS

Patient Characteristics

Cancer survivors versus controls. Cancer survivors and controls were comparable with respect to sex, age, body mass index, employment status, self-reported exercise, smoking history, and heart failure (Table 1). Controls were more likely to be non-Hispanic white (51.2% *v* 37.2%; $P < .01$) and to have health insurance (93.0% *v* 71.9%; $P < .01$).

Cancer survivors. Primary diagnoses (Table 1) included Hodgkin lymphoma (33.9%), acute lymphoblastic leukemia (16.5%), acute myeloid leukemia (14.1%), and other diagnoses (35.5%); year of cancer diagnosis ranged from 1972 to 2007. Nearly half (48.0%) had been treated with a combination of chest radiation and pulmonary-toxic chemotherapy; 52.9% had undergone HCT, and 29.5% of allogeneic HCT recipients had a history of cGVHD. However, none of the study participants had pulmonary involvement, and only 15.3% of the allogeneic HCT recipients were receiving systemic therapy for cGVHD at t2.

Pulmonary Dysfunction

Cancer survivors versus controls. Cancer survivors were significantly more likely to have restrictive defects (24.0% *v* 4.8%; $P < .01$)

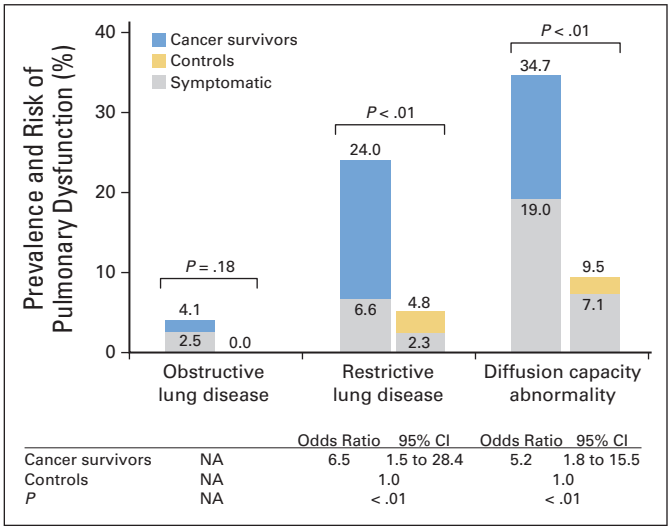


Fig 1. Prevalence and risk of pulmonary dysfunction in childhood cancer survivors versus healthy controls. Multivariable regression was adjusted for race/ethnicity, insurance status, smoking history, and cardiomyopathy and/or heart failure. NA, not applicable.

and diffusion capacity abnormalities (34.7% *v* 9.5%; $P < .01$) when compared with controls (Fig 1); there was no statistically significant difference in the prevalence of obstructive lung disease between the two groups (4.1% *v* 0%; $P = .18$). Compared with controls, cancer survivors were significantly more likely to be symptomatic (21.5% *v* 4.7%; $P < .01$; Table 2); symptomatic disease was most prevalent in survivors with diffusion defects (Fig 1). Survivors with pulmonary dysfunction had significantly poorer HRQOL across all domains when compared with survivors without dysfunction, as well as healthy controls (Table 2).

In multivariable logistic regression analysis adjusted for race/ethnicity, health insurance status, smoking history, and history of cardiomyopathy and/or heart failure, the odds of restrictive defects were increased 6.5-fold among cancer survivors when compared with controls (Fig 1). The odds of diffusion defects were increased 5.2-fold among cancer survivors when compared with controls (Fig 1).

Cancer survivors. The prevalence of any pulmonary dysfunction (obstructive, restrictive, and/or diffusion defects) among survivors was 45.5%.

Restrictive defects. Multivariable logistic regression analysis revealed younger age (< 16 years) at diagnosis (odds ratio [OR], 3.0; 95% CI, 1.2 to 7.8; $P = .02$) and exposure to higher (> 20 Gy) radiation dose (OR, 5.6; 95% CI, 1.8 to 15.5; $P = .02$; referent, no radiation) to be associated with restrictive defects (Table 3). There were no differences in self-reported pulmonary symptoms (Appendix Table A2, online only) or HRQOL (Fig 2A) between survivors with and without restrictive defects.

Diffusion defects. The odds of diffusion defects were increased 3.9-fold among females compared with males (OR, 3.9; 95% CI, 1.7 to 9.5; $P < .01$). There was a dose-dependent association with radiation exposure (referent, no radiation; ≤ 20 Gy: OR, 6.4; 95% CI, 1.7 to 24.4; $P < .01$; > 20 Gy: OR, 11.3; 95% CI, 2.6 to 49.5; $P < .01$; Table 3). Importantly, survivors with diffusion defects were significantly more likely to be symptomatic (35.7% *v* 13.9%; $P < .01$; Appendix Table A3, online only) and to have poorer HRQOL scores in the following domains: physical functioning (76.5 *v* 88; $P < .01$), role limitation as a result of physical health (70.9 p *v* 89.3; $P = .02$), and low energy/increased fatigue (45.0 *v* 59.0; $P < .01$) when compared with survivors without diffusion defects (Fig 2B).

Predictors of Decline in Lung Function

Among the 95 childhood cancer survivors with no evidence of restrictive lung disease at baseline (t1), only seven (7.4%) developed subsequent restrictive disease at t2. Conversely, among the 89 survivors with no evidence of diffusion defects at baseline (t1), 23 (25.8%) had diffusion defects at t2 (Fig 3). Female sex (OR, 4.5; 95% CI, 1.8 to 7.6; $P = .02$) and higher radiation dose (> 20 Gy: OR, 24.4; 95% CI, 5.7 to 38.3; $P < .01$; referent, no radiation) were associated with a decline in diffusion defects over time.

Blood Biomarkers

This study failed to demonstrate a significant correlation between PFT indices (obstructive [FEV_1/FVC], restrictive [TLC], or diffusion [DL_{COcorr}]) and selected blood biomarkers of lung injury (TGF-β1, PDGF-A, PDGF-B, SP-A, SP-D; Appendix Table A4, online only).

Table 2. HRQOL in Survivors With Pulmonary Dysfunction Compared With Survivors Without Pulmonary Dysfunction and Controls

	Survivors With Pulmonary Dysfunction* (n = 54)		Survivors Without Pulmonary Dysfunction (n = 62)		Controls (n = 39)		
SF-36 Domains	Mean	SD	Mean	SD	Mean	SD	*P*
General health	52.3	21.4	59.1	22.3	77.9	16.4	< .01
Physical functioning	71.3	27.2	87.4	17.9	96.2	9.7	< .01
Role limitations due to physical health	69.9	35.1	87.7	22.3	95.4	17.3	< .01
Role limitations due to emotional problems	73.8	43.0	80.0	35.8	99.1	5.3	< .01
Low energy/increased fatigue	48.2	24.8	57.1	23.0	64.9	17.4	< .01
Emotional well-being	67.5	22.4	71.1	19.9	80.3	12.1	< .01
Social functioning	75.9	25.4	81.9	23.6	96.0	7.7	< .01
Pain	73.2	27.0	82.3	18.4	91.6	11.4	< .01

NOTE. Analysis was limited to symptomatic childhood cancer survivors (n = 116) and healthy controls (n = 39) who were age18 years or older at study enrollment.
Abbreviations: HRQOL, health-related quality of life; SF-36, Medical Outcomes Study 36-Item Short-Form Health Survey; SD, standard deviation.
*Defined as obstructive lung disease, restrictive lung disease, or diffusion capacity abnormality.

Table 3. Risk of Restrictive or Diffusion Abnormalities Among Childhood Cancer Survivors According to Demographic Characteristics, Lifestyle, and Treatment-Related Variables

	Restrictive Lung Disease (n = 29)		No Restrictive Lung Disease (n = 92)		Univariable Regression		Multivariable Regression		Diffusion Abnormality (n = 42)		No Diffusion Abnormality (n = 79)		Univariable Regression		Multivariable Regression	
Characteristic	No.	%	No.	%	OR	95% CI	OR	95% CI	No.	%	No.	%	OR	95% CI	OR	95% CI
Sex																
Male	15	51.7	46	50.0	1.0		—		12	28.6	49	62.0	1.0		1.0	
Female	14	48.3	46	50.0	0.9	0.4 to 2.2	—		30	71.4	30	38.0	4.1*	1.8 to 9.2	3.9*	1.7 to 9.5
Race/ethnicity																
Non-Hispanic white	11	37.9	34	37.0	1.0		—		19	45.2	26	32.9	1.0		—	
Hispanic	12	41.4	47	51.1	0.8	0.3 to 2.0	—		16	38.1	43	54.4	0.5	0.2 to 1.2	—	
Other	6	20.7	11	12.0	1.7	0.5 to 5.6	—		7	16.7	10	12.7	1.0	0.3 to 3.0	—	
BMI at examination, kg/m^2																
< 25	16	55.2	50	54.3	1.0		—		27	64.3	29	36.7	1.0		1.0	
≥ 25	13	44.8	42	45.7	1.0	0.4 to 2.2	—		15	35.7	50	50.6	0.5	0.3 to 1.2	0.5	0.2 to 1.1
Employment																
Employed	19	65.5	62	68.9	1.0		—		29	69.0	52	67.5	1.0		—	
Unemployed	10	34.5	30	32.6	1.2	0.5 to 2.8	—		13	31.0	27	34.2	0.9	0.4 to 2.1	—	
Insurance status																
Insured	19	65.5	68	73.9	1.0		—		29	69.0	58	73.4	1.0		—	
Uninsured	10	34.5	24	26.1	1.5	0.6 to 3.7	—		13	31.0	21	26.6	1.2	0.5 to 2.8	—	
Exercise, days per week																
≥ 3	18	62.1	53	57.6	1.0		—		31	73.8	57	72.2	1.0		—	
< 3	11	37.9	39	42.4	0.8	0.4 to 2.0	—		11	26.2	22	27.8	1.1	0.5 to 2.3	—	
Smoking history																
Never	28	96.6	87	94.6	1.0		—		40	95.2	75	94.9	1.0		—	
Ever	1	3.4	5	5.4	0.9	0.7 to 1.9	—		2	4.8	4	5.1	0.9	0.2 to 5.3	—	
Diagnosis																
Lymphoma	11	37.9	37	40.2	1.0		—		16	38.1	32	40.5	1.0		—	
Leukemia	12	41.4	36	39.1	1.1	0.4 to 2.9	—		18	42.9	30	38.0	1.2	0.5 to 2.8	—	
Solid malignancy	6	20.7	19	20.7	1.1	0.3 to 3.3	—		8	19.0	17	21.5	0.9	0.3 to 2.7	—	
Age at diagnosis, years																
≥ 16	10	34.5	52	56.5	1.0		1.0		21	50.0	42	53.2	1.0		—	
<16	19	65.5	40	43.5	2.5†	1.0 to 5.9	3.0†	1.2 to 7.8	21	50.0	37	46.8	1.1	0.5 to 2.4	—	
Time since diagnosis, years																
< 17	14	48.3	46	50.0	1.0		—		18	42.9	42	53.2	1.0		—	
≥ 17	15	51.7	46	50.0	1.1	0.5 to 2.5	—		24	57.1	37	46.8	1.5	0.7 to 3.2	—	
Cardiomyopathy																
No	27	93.1	86	93.5	1.0		—		39	90.7	75	94.9	1.0		—	
Yes	2	6.9	6	6.5	1.1	0.2 to 5.6	—		4	9.3	4	5.1	2.0	0.5 to 8.3	—	

(continued on following page)

Table 3. Risk of Restrictive or Diffusion Abnormalities Among Childhood Cancer Survivors According to Demographic Characteristics, Lifestyle, and Treatment-Related Variables (continued)

Characteristic	Restrictive Lung Disease (n = 29)		No Restrictive Lung Disease (n = 92)		Univariable Regression		Multivariable Regression		Diffusion Abnormality (n = 42)		No Diffusion Abnormality (n = 79)		Univariable Regression		Multivariable Regression	
	No.	%	No.	%	OR	95% CI	OR	95% CI	No.	%	No.	%	OR	95% CI	OR	95% CI
Treatment details																
Bleomycin, IU/m^2																
Median	70.5		60				—		70.5		60					
Range	34-120		30-360						34-120		30-360					
None	21	72.4	58	63.0	1.0		—		29	69.0	50	63.3	1.0		—	
Any	8	27.6	34	37.0	0.7	0.3 to 1.6	—		13	31.0	29	36.7	0.8	0.4 to 1.7	—	
Busulfan, mg/m^2																
Median	480		436				—		480		436				—	
Range	480-770		310-1,102						480-770		310-1,102					
None	26	89.7	80	87.0	1.0		—		39	92.8	67	84.8	1.0		—	
Any	3	10.3	12	13.0	0.8	0.2 to 2.9			3	7.1	12	15.2	0.4	0.1 to 1.6	—	
BCNU or CCNU, mg/m^2																
Median	450		450				—		450		450				—	
Range	225-450		300-987						225-450		300-987					
None	26	89.7	83	90.2	1.0		—		37	88.1	72	91.1	1.0		—	
Any	3	10.3	9	9.8	1.1	0.3 to 4.2	—		5	11.9	7	8.9	1.4	0.6 to 4.7	—	
Chest radiation therapy, Gy																
None	4	13.8	28	30.4	1.0		1.0		3	7.1	29	36.7	1.0		1.0	
≤ 20	13	44.8	47	51.1	1.5	0.4 to 5.8	1.6	0.5 to 5.7	24	57.1	36	45.6	6.4*	1.8 to 23.6	6.4*	1.7 to 24.4
> 20	12	41.4	17	18.5	4.9†	1.4 to 17.8	5.6†	1.5 to 21.0	15	35.7	14	17.7	10.4*	2.6 to 41.8	11.3*	2.6 to 49.5
HCT																
None	12	41.4	45	48.9					18	42.9	39	49.4	1.0		—	
Autologous	4	13.8	16	17.4					7	16.7	13	16.5	1.2	0.4 to 3.4	—	
Allogeneic	13	44.8	31	33.7					17	40.5	27	34.2	1.4	0.6 to 3.1	—	

Abbreviations: BCNU, carmustine; BMI, body mass index; CCNU, chloroethylcyclohexylnitrosourea; HCT, hematopoietic cell transplantation; OR, odds ratio.
*$P < .01$.
†$P < .05$.

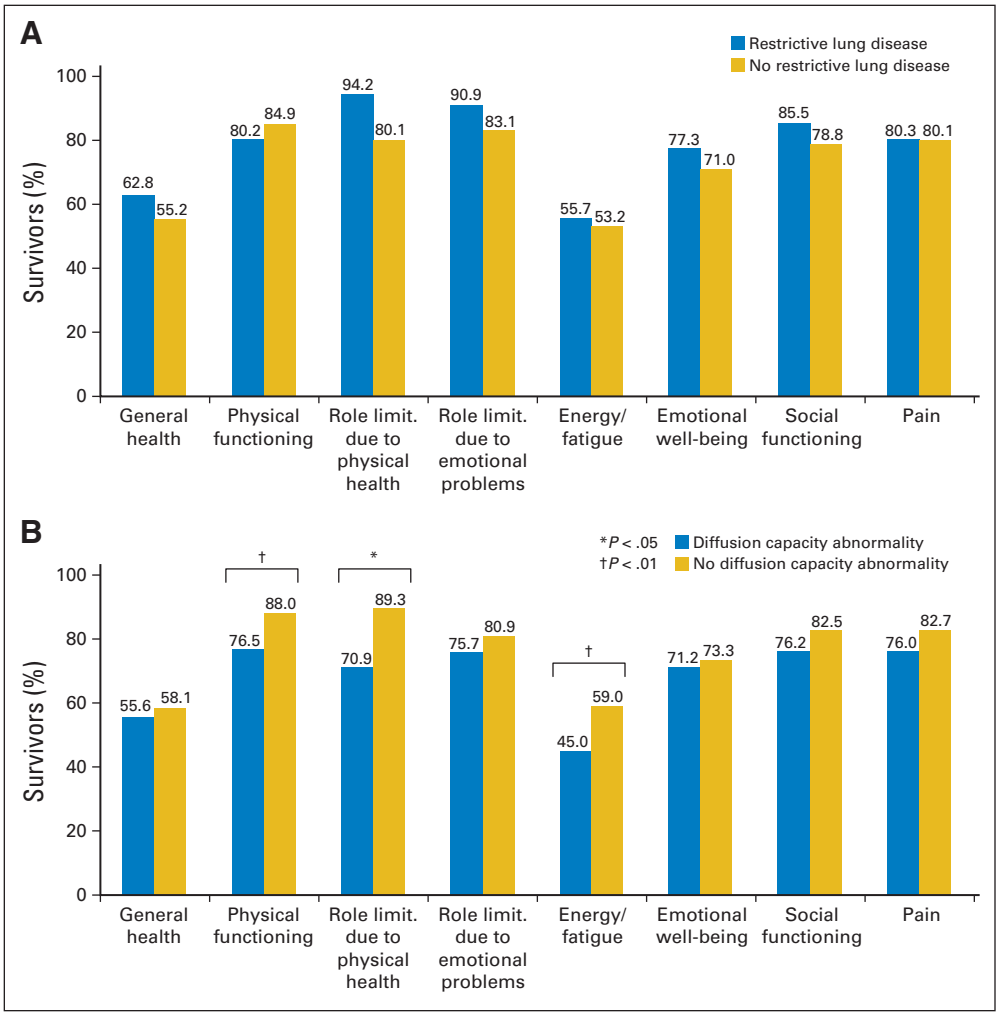


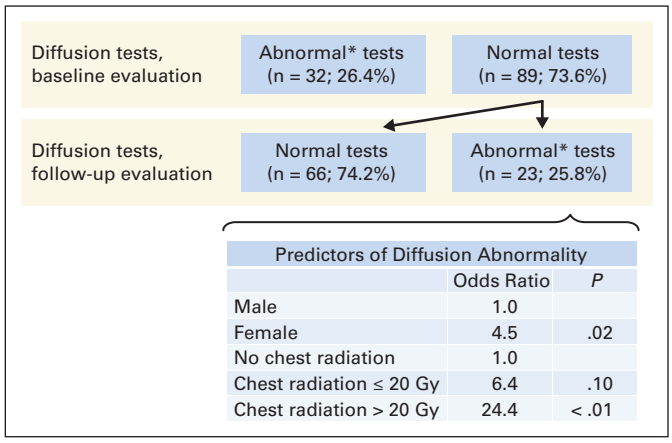
Fig 2. Health-related quality of life in childhood cancer survivors with (A) restrictive lung disease or (B) diffusion capacity abnormality compared with those without. Analysis was limited to childhood cancer survivors (n = 116) who were age 18 years or older at study enrollment. limit., limitation.

DISCUSSION

The growing population of childhood cancer survivors has brought to the forefront several questions related to the modality, frequency, and duration of screening for therapy-related late effects. Recent cross-sectional screening studies[6,7] have found pulmonary dysfunction to be the most prevalent complication in long-term childhood cancer survivors. However, it is not known whether these abnormalities are associated with symptoms or poor HRQL or whether pulmonary function continues to decline over time. Furthermore, the utility of blood biomarkers of lung injury for surveillance is not established. In this study, comprehensive profiling of childhood cancer survivors at risk for pulmonary dysfunction revealed increased odds of having symptomatic lung disease when compared with controls and a significant association between pulmonary dysfunction and worse HRQOL. Decline in lung function over time was largely a result of changes in diffusion capacity; the odds of decline in pulmonary function were greater than four-fold in females treated with pulmonary-toxic therapy and were twenty-four–fold among cancer survivors treated with higher (> 20 Gy) radiation dose.

Previous studies have reported wide-ranging (20% to 100%) prevalence for pulmonary dysfunction in childhood cancer survivors,[2] attributed in part to differences in screening strategies used by each study. In this study, screening for pulmonary dysfunction was limited to survivors at risk according to COG LTFU Guidelines. Recent studies[6,7] that used the same screening criteria reported a higher prevalence of pulmonary dysfunction (> 65%) than that found in this study (45%). However, it is important to note that these studies were more inclusive (all levels of severity were included); comparable definition of pulmonary dysfunction would have yielded an overall prevalence of 62% in this study. The more stringent criteria used in this study yielded a prevalence that was comparable (44%) to that reported by Mulder et al[8] who used the same criteria for pulmonary dysfunction in childhood cancer survivors.

Compared with healthy controls, childhood cancer survivors had five times the odds of diffusion capacity abnormality, seven times the odds of restrictive lung disease, and five times the odds of reporting pulmonary symptoms, which highlights the substantial burden of pulmonary disease in this population. Conversely, we found no association between candidate blood markers of lung injury and indices of pulmonary dysfunction. This lack of association may be the result of a combination of both the timing of the assessment and reliance on biomarkers of acute lung injury included in the study.



Predictors of Diffusion Abnormality		
	Odds Ratio	*P*
Male	1.0	
Female	4.5	.02
No chest radiation	1.0	
Chest radiation ≤ 20 Gy	6.4	.10
Chest radiation > 20 Gy	24.4	< .01

Fig 3. Prevalence of diffusion abnormalities at entry into Long-Term Follow-Up clinic and predictors of decline at follow-up. (*) Diffusing capacity of the lungs for carbon monoxide (corrected for hemoglobin content, age, and sex) less than 75% predicted.

Restrictive lung disease in childhood cancer survivors is characterized by reduced lung volumes as a result of either reduction in lung parenchyma or changes to the chest wall that may restrict lung parenchymal growth.[1,2] These changes are likely a result of exposure to chest radiation at a young age, resulting in disturbance in normal growth and development,[1,2] and the findings from this study support this phenomenon. However, little is known regarding the impact of these changes on HRQOL, and little is known regarding the trajectory of lung function over time. In this study, there were no differences in self-reported symptoms or HRQOL between survivors with and without restrictive lung disease. Moreover, the vast majority (93%) of the survivors without restrictive disease at baseline retained intact pulmonary function, indicating that new restrictive changes are unlikely to develop in a young adult (median age, 32 years) population more than 15 years after completion of therapy.

Diffusion capacity abnormality can result from radiation involving the lung parenchyma; exposure to bleomycin, busulfan, and nitrosoureas; or as a complication of GVHD.[1,2,24] We found a dose-dependent association with radiation exposure, and female survivors had nearly four times the odds of diffusion capacity abnormality when compared with males, independent of radiation exposure. Survivors with diffusion capacity abnormality were significantly more likely to report respiratory symptoms and poor physical functioning as well as low energy and increased fatigue when compared with those with normal diffusion. Importantly, one in four survivors with intact diffusion capacity at baseline demonstrated a decline in function over time, and nearly half reported respiratory symptoms at t2, which emphasizes the importance of longitudinal follow-up that includes PFT measures of diffusion capacity.

The results of our studies, unlike those of previous studies,[2,8,25,26] did not reveal an association between cumulative chemotherapy dose and diffusion capacity abnormality. This may be the result of exposure to relatively low doses of certain chemotherapy agents such as bleomycin (median, 60 IU/m^2) in the study population (high risk,[2,8,27] typically defined as $>$ 300 mg/m^2), and the small proportion of individuals (12.3%) treated with busulfan and/or nitrosoureas. It is important to note that only patients deemed to be at risk according to the COG LTFU Guidelines were screened. Thus, this study did not investigate associations with therapeutic exposures not consistently shown to cause long-term pulmonary toxicity. Furthermore, we did not capture detailed information on radiation dosimetry, including volume of the lungs irradiated as well as dose to parts of the lungs and chest wall. This limitation notwithstanding, it is important to note that in the community setting, health care providers caring for childhood cancer survivors typically do not have detailed information on lung dosimetry, relying instead on dose delivered to a treatment field to determine screening practices. The approach used in this study aligned with the approaches of other more recent studies[7,8] that evaluated pulmonary outcomes in long-term childhood cancer survivors. With regard to our finding that females treated with pulmonary-toxic therapies were more likely to have diffusion capacity abnormality when compared with males, there is a large body of evidence supporting female predisposition to several health-related complications (cardiomyopathy, metabolic syndrome, osteonecrosis, hypothyroidism) among childhood cancer survivors[28]; the underlying cause(s) of this increased risk have not been uniformly elucidated.[28] To the best of our knowledge, this study is the first to identify the association between female sex and pulmonary dysfunction. Further investigation is needed to validate these findings and to explore the pathogenesis of these differences.

In summary, comprehensive profiling of childhood cancer survivors who received potentially pulmonary-toxic therapy identified a high risk of symptomatic moderate-to-severe pulmonary dysfunction several years after completion of therapy. Moreover, certain subsets of patients continue to be at risk for declining pulmonary function over time, highlighting the need for continued vigilance beyond the recommended baseline screening visit. These findings may facilitate the development of targeted screening approaches for patients at high risk for progressive pulmonary disease such as diffusion capacity abnormality, setting the stage for the development of therapeutic[29,30] or lifestyle interventions[31,32] to improve pulmonary function in survivors at highest risk for symptomatic respiratory comorbidities.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Long-Term Pulmonary Function in Survivors of Childhood Cancer

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Appendix

Table A1. Patient and Treatment Characteristics and Prevalence of Abnormal PFTs at Baseline for Study Participants and Nonparticipants

Characteristic	Participants (n = 121)		Nonparticipants (n = 34)		*P*
	No.	%	No.	%	
Male sex	61	50.4	22	64.7	.14
Race/ethnicity					
Non-Hispanic white	45	37.2	18	52.9	.25
Hispanic	59	48.8	13	38.2	
Other	17	14.0	3	8.8	
Hematologic diagnosis	88	72.7	25	75.8	.78
Age at diagnosis, years					
Median	16.5		16.9		.90
Range	0.2-21.9		0.5-21.7		
Cardiomyopathy	8	6.6	4	11.8	.32
Treatment details					
Bleomycin					.80
Median	60		60		
Range	30-360		16-170		
Any	42	34.7	14	41.2	.49
Busulfan					
Median	436		1,178		.52
Range	115-1,102		436-1,920		
Any	15	12.4	2	5.9	.28
BCNU/CCNU					
Median	450		525		.81
Range	225-987		450-600		
Any	12	9.9	2	5.9	.47
Radiotherapy, Gy					
Median	13.2		21.2		.91
Range	2-76		10-40		
None	32	26.4	11	32.4	.78
≤ 20	60	49.6	15	44.1	
> 20	29	24.0	8	23.5	
Lobectomy, metastectomy, wedge resection	7	5.8	2	5.9	.98
HCT					
None	57	47.1	16	47.1	.58
Autologous	20	16.5	8	23.5	
Allogeneic	44	36.4	10	29.4	
Age at baseline PFT, years					.43
Median	27.16		29.8		
Range	10.4-54.9		11.4-45.4		
Time since diagnosis to baseline PFT, years					
Median	12.1		15.3		.30
Range	4.3-36.1		5.2-36.5		
Lung function					
Obstructive lung disease, $FEV_1/VC < 0.7$ and $FEV_1 < 80\%$	6	5.0	3	8.8	.40
Restrictive lung disease, TLC < 75% predicted and $FEV_1 \geq 80\%$	26	21.5	7	20.6	.91
Diffusion capacity abnormality, DL_{COcorr} and/or $DL_{CO}/V_A < 75\%$ predicted	32	26.4	10	23.4	.73

Abbreviations: BCNU, carmustine; CCNU, chloroethylcyclohexylnitrosourea; DL_{COcorr}, diffusing capacity of the lungs for carbon monoxide (corrected for hemoglobin content, age, and sex); DL_{CO}/V_A, diffusing capacity of the lungs for carbon monoxide divided by volume of air; FEV_1, forced expiratory volume in 1 second; HCT, hematopoietic cell transplantation; PFT, pulmonary function test; TLC, total lung capacity; VC, ventilator capacity.

Table A2. Self-Reported Pulmonary Symptoms in Cancer Survivors With or Without Restrictive Lung Disease

Self-Reported Symptoms*	Restrictive Lung Disease (n = 29) No.	%	No Restrictive Lung Disease (n = 92) No.	%	*P*
Are you troubled by shortness of breath when hurrying on ground level or walking up a slight hill?	10	34.5	23	25.0	.32
Do you notice shortness of breath walking with other people of your own age on level ground?	6	20.7	17	18.5	.79
Do you have to stop for breath when walking at your own pace on level ground?	4	13.8	6	6.5	.22
Are you short of breath when washing or dressing?	1	3.4	8	8.7	.35
Are you short of breath at rest?	1	3.4	4	4.3	.83
Symptomatic†	7	24.1	19	20.7	.69

*As assessed from the Medical Research Council (MRC) Dyspnea Questionnaire.
†Defined as having responded "yes" to any two of the MRC Dyspnea Questionnaire items.

Table A3. Self-Reported Pulmonary Symptoms in Cancer Survivors With or Without Diffusion Abnormalities

Self-Reported Symptoms*	Diffusion Capacity Abnormality (n = 42) No.	%	No Diffusion Capacity Abnormality (n = 79) No.	%	*P*
Are you troubled by shortness of breath when hurrying on ground level or walking up a slight hill?	19	45.2	14	17.7	< .01
Do you notice shortness of breath walking with other people of your own age on level ground?	12	28.6	11	13.9	.05
Do you have to stop for breath when walking at your own pace on level ground?	5	11.9	5	6.3	.29
Are you short of breath when washing or dressing?	4	9.5	5	6.3	.52
Are you short of breath at rest?	2	4.8	3	3.8	.80
Symptomatic†	15	35.7	11	13.9	.01

*As assessed from the Medical Research Council (MRC) Dyspnea Questionnaire.
†Defined as having responded "yes" to any two of the MRC Dyspnea Questionnaire items.

Table A4. Pearson Correlation Between Blood Biomarkers and Indices of Obstructive (FEV_1/FVC), Restrictive (TLC), and Diffusion (DL_{CO}) Abnormalities

Variable	TGF-β1	*P*	PDGF-A	*P*	PDGF-B	*P*	SP-A	*P*	SP-D	*P*
Cancer survivors and controls (n = 163)										
FEV_1/FVC	–0.07	.35	–0.02	.83	–0.05	.56	0.09	.23	0.03	.71
TLC	–0.16	.04	–0.09	.24	–0.07	.35	0.03	.73	0.03	.67
DL_{COcorr}	–0.16	.04	–0.07	.38	–0.08	.30	0.11	.18	0.08	.32
Cancer survivors (n = 121)										
FEV_1/FVC	–0.11	.22	–0.05	.62	–0.09	.31	0.15	.11	0.06	.53
TLC	–0.06	.51	–0.06	.50	0.01	.89	–0.08	.40	–0.05	.61
DL_{COcorr}	–0.08	.38	0.03	.76	0.03	.76	0.02	.87	0.03	.77

Abbreviations: DL_{CO}, diffusing capacity of the lungs for carbon monoxide; DL_{COcorr}, DL_{CO} corrected for hemoglobin content, age, and sex; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PDGF-A/B, platelet-derived growth factor A/B; SP-A/D, surfactant proteins A and D; TGF-β1, tumor growth factor beta1; TLC, total lung capacity.

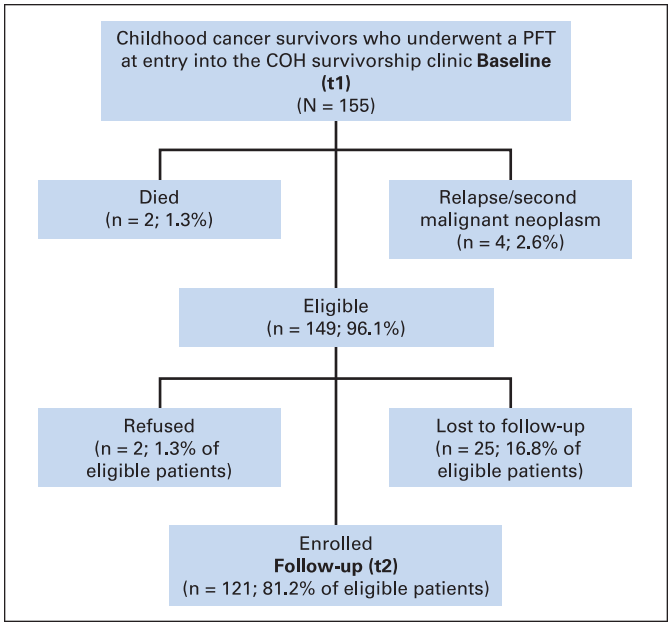

Fig A1. Study flow diagram demonstrating recruitment of the 155 childhood cancer survivors who underwent a pulmonary function test (PFT) at entry into the City of Hope (COH) survivorship clinic.