

Pulmonary Dysfunction after Treatment for Childhood Cancer: Comparing Multiple-Breath Washout with Spirometry

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Abstract

Rationale: Childhood cancer survivors are at risk of long-term pulmonary dysfunction, but we lack sensitive outcome measures to detect early pulmonary damage.

Objective: To assess the ability of nitrogen multiple-breath washout (N_2 MBW) for detecting pulmonary dysfunction compared to spirometry in long-term survivors of childhood cancer.

Methods: We analyzed cross-sectional data from long-term (≥ 5 -year) survivors of childhood cancer, aged ≤ 16 years at cancer diagnosis, ≥ 16 years at study (assessment period 2015-2019).

We categorized survivors by risk: high risk for those having had pulmotoxic chemotherapy, chest radiation, thoracic surgery, and/or hematopoietic stem cell transplantation, and standard risk for other cancer therapies. Primary outcomes were the global lung clearance index (LCI) and acinar ventilation inhomogeneity index (S_{ACIN}) from N_2 MBW, and forced expiratory volume in one second (FEV_1) and functional vital capacity (FVC) from spirometry. We calculated z scores for N_2 MBW and spirometry parameters and compared pulmonary dysfunction between risk groups. Pulmonary dysfunction was defined as z score $+1.64$ for N_2 MBW and -1.64 for spirometry.

Results: We studied 46 survivors, median age at diagnosis 10 years (interquartile range [IQR] 4-14), median age at study 30 years (IQR 25-40). Thirty-seven percent were at high risk and 63% at standard risk for pulmonary dysfunction. LCI and S_{ACIN} were higher in the high risk group compared to the standard risk group (mean LCI z scores 2.09, standard deviation [SD] 2.39 vs 0.95, SD 2.81; mean S_{ACIN} z scores 2.45, SD 3.29 vs 0.65, SD 2.79). FEV_1 and FVC were lower in the high risk compared to the standard risk group (mean FEV_1 z scores -0.94 , SD 1.39 vs -0.10 , SD 1.07; mean FVC z scores -1.14 , SD 1.23 vs 0.15, SD 1.61). Overall, LCI, S_{ACIN} , FEV_1 , and FVC

were abnormal in 60%, 53%, 33%, and 33% of high risk patients compared to 23%, 21%, 0%, and 4% of standard risk patients.

Conclusions: N₂MBW identified more cases of pulmonary dysfunction in long-term survivors of childhood cancer than spirometry, even in patients who had cancer therapy not specifically known as being pulmotoxic. N₂MBW could be a complementary screening tool for early pulmonary damage after treatment for childhood cancer.

Clinical trial registered with ClinicalTrials.gov (NCT02730767).

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Pulmotoxic cancer treatment can cause long-term pulmonary damage (1, 2) leading to a 15-fold increased mortality compared to the general population (3). There is clear evidence for pulmotoxicity for some treatments such as bleomycin and chest radiation for which guidelines recommend surveillance (4). A number of other chemotherapies are suspected of damaging the lungs (5-9), but solid data are lacking. Because symptomatic disease occurs relatively late due to the large functional reserve of the lungs and a long silent period (10), early screening for functional changes is necessary.

Spirometry currently is recommended for screening childhood cancer survivors (4) even though it mainly measures changes in the large airways and is insensitive to small airway damage potentially caused by cancer treatment. Increasingly, though, nitrogen multiple-breath washout (N_2 MBW) is being used to measure ventilation inhomogeneity and small airway disease (11). Its main outcome indices are the lung clearance index (LCI), a marker for global ventilation inhomogeneity, and the acinar ventilation inhomogeneity index (S_{ACIN}), which measures global and acinar ventilation inhomogeneity. N_2 MBW is more sensitive than spirometry for the detection of early pulmonary disease in children with cystic fibrosis (12, 13), in pediatric patients undergoing hematopoietic stem cell transplantation (HSCT) (14) and lung transplantation (15), and in adults after HSCT (14, 16). It has not yet been used with childhood cancer survivors.

Pulmotoxic chemotherapy (17), chest radiation (18), and HSCT can damage the alveolar, vascular, and parenchymal lung compartments. The histopathological process involves inflammation where cytokines and growth factors stimulate collagen production by fibroblasts, leading to lung fibrosis (Figure 1) (18). Initially, this damage occurs in the small airway

compartments, resulting in reduced ventilation of the lung periphery and impaired diffusion. The N₂MBW could be a sensitive test to assess ventilation inhomogeneity resulting from early fibrotic damage. As the fibrosis progresses, also larger airways may be damaged, resulting in airway obstruction and restriction, which can be measured with spirometry. Previous studies in childhood cancer survivors have shown signs of reduced lung volumes and reduced oxygen diffusion capacity, which are both indicative for fibrosis, but only very few survivors had signs of airway obstruction (19). To the best of our knowledge, no previous study in childhood cancer survivors has used the N₂MBW test to assess early pulmonary damage. Since lung fibrosis starts in the smaller airways, we hypothesized that N₂MBW would detect more cases of pulmonary dysfunction than spirometry. We further hypothesized that high risk survivors would show more pulmonary dysfunction than standard risk survivors of childhood cancer. This study measured pulmonary function in adult survivors of childhood cancer, and it compared N₂MBW and spirometry results in high risk survivors exposed to confirmed pulmotoxic treatment and standard risk survivors treated with other cancer therapies.

Methods

Study Design and Study Population

We enrolled childhood cancer survivors participating in the SURfit study (20). SURfit is a randomized controlled, physical activity intervention study conducted between 2015 and 2019 at the University Children's Hospital Basel, Switzerland. Participants were recruited through the Swiss Childhood Cancer Registry, a nationwide registry of all patients diagnosed with leukemia,

lymphoma, central nervous system tumors, malignant solid tumors, or Langerhans cell histiocytosis before age 21 years in Switzerland (21). Inclusion criteria for SURfit were age ≤ 16 years at cancer diagnosis, survival of five years or more since cancer diagnosis, and age at study ≥ 16 years. Participants were randomized 1:1 to an intervention group with 2.5 hours of physical activity per week additional to individual baseline activity, and a control group with continuation of individual baseline activity.

We conveniently sampled participants from two risk groups for pulmonary dysfunction: 1) high risk for pulmonary dysfunction due to exposure to established pulmotoxic cancer treatments including busulfan, bleomycin, carmustine, lomustine, chest radiation, thoracic surgery, and/or HSCT (4), and 2) standard risk for pulmonary dysfunction due to other chemotherapies (5-9, 22). Within these groups, we recruited SURfit participants who agreed to undergo additional pulmonary function assessment. Pulmonary function was measured cross-sectionally three months after randomization in the SURfit study for organizational reasons. We did not expect any change of pulmonary function in survivors who increased their physical activity levels due to the intervention. Nevertheless, we adjusted for study group in a sensitivity analysis.

Ethics approval was granted by the Swiss Ethics Committee on research involving humans (Ethikkommission Nordwest- und Zentralschweiz [EKNZ], reference number: EKNZ-2015-169), and the SURfit study was registered at ClinicalTrials.gov (identifier: NCT02730767).

Nitrogen Multiple-Breath Washout

Pulmonary function was measured by one experienced technician in a specialized pulmonary function laboratory at the University Children's Hospital Basel, Switzerland. The technician was blinded to the risk group of survivors. All N₂MBW measurements were performed according to the European Respiratory Society and American Thoracic Society consensus statement (23) on the same commercially available device (Exhalyzer D, Spiroware 3.1.6, Eco Medics AG). Main N₂MBW indices were LCI, conductive ventilation inhomogeneity index (S_{COND}), S_{ACIN} , and functional residual capacity (FRC). We calculated z scores using published reference values from healthy adults (24).

Spirometry

Spirometry was performed after N₂MBW using the same Jaeger MasterScreen (CareFusion, Hochberg, Germany) device according to the European Respiratory Society and American Thoracic Society consensus statement (25). Main spirometry indices were forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), and the Tiffenau index (FEV₁/FVC). We calculated z scores using the Global Lung Function Initiative (GLI) reference equations (26).

Risk Group Stratification

We categorized survivors by risk: high risk for those having had pulmotoxic chemotherapy (bleomycin, busulfan, cardmustine, lomustine), HSCT, chest radiation (mediastinal/lung radiation, cranio-spinal radiation, and total body irradiation), and/or thoracic surgery (4), and

standard risk for other cancer therapies. We further stratified high risk survivors into survivors with and without HSCT.

Defining Covariates

We assessed demographic characteristics at study entry and collected information on cancer diagnosis and treatment from medical records. Anthropometric measures were collected at the time of pulmonary function assessment as previously reported (20).

Statistical Analysis

Data were expressed in mean \pm standard deviation (SD) or median and interquartile range (IQR) as appropriate. Upper limits of normality (ULN) were defined as z score +1.64 for LCI, FRC, S_{COND} , and S_{ACIN} . Lower limits of normality (LLN) were defined as z score -1.64 for FEV_1 and FVC, and as <0.7 for FEV_1/FVC (26). We used chi-squared and t-tests to compare demographic and clinical characteristics, and pulmonary function as appropriate in high vs standard risk survivors. With univariable and multivariable linear regression models, we investigated the association between pulmonary risk groups (high vs standard risk) and pulmonary function parameters, controlling for potential confounders. We adjusted for age, sex, weight, height, and active smoking status. In a sensitivity analysis, we added intervention group and time since diagnosis to the multivariable model to investigate the possible effects of increased physical activity or time since diagnosis on pulmonary function parameters. We used STATA software (Version 15.1, StataCorporation, Austin, TX).

Results

Study Population

The SURfit study included 162 survivors overall, 46 of whom (28%) were recruited for pulmonary function assessment. Complete characteristics of the assessed survivors are presented in Table 1, and the flowchart in Figure E1 illustrates the allocation of survivors into the high and standard risk groups. Among the assessed survivors, median age at diagnosis was 10 years (interquartile range [IQR] 4–14), median age at study 30 years (IQR 25–40), and median time since diagnosis 20 years (IQR 15–32). Over half of the survivors had been treated for leukemia and one-quarter for lymphoma, all but two survivors (96%) had received chemotherapy, and half of the 46 assessed survivors had undergone radiotherapy. Seventeen of the assessed survivors (37%) belonged to the high risk and 29 (63%) to the standard risk group. In the high risk group, 15 survivors (88%) had received chest radiation with a median cumulative dose of 20 Gray, nine survivors (53%) received mediastinal/lung radiation, two survivors (12%) cranio-spinal radiation, and four survivors (24%) total body irradiation. The high and standard risk groups differed by age at diagnosis and by weight at lung function, and 11 high risk and 13 standard risk patients were in the physical intervention group. At the time of study, none of the survivors reported asthma or any other pre-existing pulmonary disease and none had chronic respiratory symptoms.

Table E1 (online supplement) compares the characteristics of all SURfit participants, with and without pulmonary function assessment. Survivors without pulmonary function assessment were younger at cancer diagnosis (median age 6 years), and a higher proportion in

the assessment group had leukemia (25 of 46 survivors, 54%) than did those in the group with no pulmonary function assessment (32 of 116, 28%).

N₂MBW Parameters

After quality control, N₂MBW indices were available for 15 of 17 high risk survivors (15 LCI and 15 S_{ACIN} indices) and 26 of 29 standard risk survivors (26 LCI and 24 S_{ACIN} indices) (Figure E1, online supplement). Overall, childhood cancer survivors had increased mean z scores for LCI, FRC, and S_{ACIN} compared to reference values, and high risk patients had higher z scores than standard risk patients (Table 2). N₂MBW indices tended to be increased as well in standard risk patients with mean z scores of 0.95 for LCI, 0.20 for FRC, and 0.65 for S_{ACIN}. Absolute LCI and S_{ACIN} values (Figures 2 and 3) illustrate that a considerable proportion of high and standard risk patients had pulmonary function indices above the ULN.

LCI and S_{ACIN} were abnormal in 60% (9 of 15 survivors) and 53% (8 of 15 survivors) of participants at high risk and in 23% (6 of 26 survivors) and 21% (5 of 24 survivors) at standard risk ($p < 0.050$) (Table 3). N₂MBW detected any abnormal value in 63% (26/41) of patients, 80% (12/15) in the high risk and 54% (14/26) in the standard risk group ($p = 0.094$).

Spirometry Parameters

After quality control, spirometry indices were available for 15 of 17 high risk survivors (15 FEV₁ and 15 FVC indices) and 23 of 29 standard risk survivors (23 FEV₁ and 23 FVC indices) (Figure E2, online supplement). Childhood cancer survivors overall and high risk survivors in particular had decreased mean z scores for FEV₁ (overall -0.43, high risk -0.94) and FVC (overall -0.36, high risk

-1.14) and preserved FEV₁/FVC ratios (overall 0.07, high risk 0.36) (Table 2). Spirometry parameters were normal in standard risk patients, with mean z scores of -0.10 for FEV₁, 0.15 for FVC, and -0.12 for FEV₁/FVC.

FEV₁ and FVC were abnormal in 33% of participants in the high risk group and in 0% and 4% of participants in the standard risk group ($p < 0.050$) (Table 3). As expected, standard risk survivors had a prevalence of abnormal spirometry comparable to the healthy reference population (5% given a defined LLN of mean z score -1.64). Overall, spirometry detected less cases of pulmonary dysfunction than N₂MBW with any abnormal parameter in 18% (7/38) of patients, 33% (5/15) in the high risk and 9% (2/23) in the standard risk group ($p = 0.055$). The proportion of participants who had both an abnormal spirometry and an abnormal N₂MBW test was $n = 4$ (24%) in the high risk group, and $n = 1$ (4%) in the standard risk group.

Association between Pulmotoxic Exposure and Pulmonary Function Parameters

In a linear regression adjusting for the possible confounders sex, age, weight, height, and active smoking status at pulmonary function assessment, we investigated the change of lung function indices when comparing high risk vs standard risk (reference) survivors (Table E2, online supplement). LCI and S_{ACIN} were higher in survivors exposed to pulmotoxic cancer treatment – LCI by 1.110 units and S_{ACIN} by 0.036 units. FEV₁ and FVC were lower in survivors exposed to pulmotoxic cancer treatment – FEV₁ by 0.239 L and FVC by 0.778 L. The physical activity intervention had no apparent effect on pulmonary function parameters. We also observed no effect of time since diagnosis on pulmonary function parameters (data not shown).

Pulmonary Function Parameters in High Risk Survivors after HSCT

Table E3 (online supplement) shows demographic and clinical characteristics, and pulmonary function abnormalities of the 17 high risk survivors, among whom five had undergone allogeneic HSCT. Four of these five HSCT survivors received total body irradiation with 12 Gray and one survivor received pulmotoxic chemotherapy with busulfan. Pulmonary function assessment was complete in four of the five HSCT survivors. All four HSCT survivors with available N₂MBW results had at least one abnormal value, whereas only one had abnormal spirometry results (Table E3, online supplement). All four of these HSCT survivors had abnormal S_{ACIN} parameters and two had abnormal LCI parameters, but only one had decreased FEV₁ and FVC (Figures 2 and 3).

Discussion

N₂MBW has to date been investigated only in pediatric cancer patients undergoing HSCT (14). This is the first study that shows results of N₂MBW tests in long-term survivors of childhood cancer. We found that more than half of childhood cancer survivors had some signs of pulmonary dysfunction. N₂-MBW detected more cases of abnormal pulmonary function than spirometry. LCI and S_{ACIN} in particular were abnormal in patients considered to be at no increased risk because they had received chemotherapy other than busulfan, bleomycin, or nitrosoureas or radiotherapy other than to the chest.

Our results are in line with other studies suggesting that N₂MBW might be a sensitive and complementary marker of pulmonary damage. A study of adult HSCT recipients from our

group showed that LCI correlated well with increasing grades of chronic graft-versus-host-disease (cGvHD), a pulmonary complication after HSCT (16). LCI and S_{ACIN} were more sensitive than spirometry in detecting abnormal pulmonary function; 74% of patients had abnormal LCI, but only 36% had abnormal FEV_1 . In the current study, 60% of high risk patients had abnormal LCI and 33% abnormal FEV_1 . A publication on lung transplant recipients reported that LCI increased with severity of bronchiolitis obliterans syndrome (27). A significant proportion of patients had abnormal LCI but not FEV_1 values, which also suggests LCI to be more sensitive than spirometry in the early detection of pulmonary disease (27). In the only study that assessed N_2 MBW in pediatric HSCT recipients who were still under active cancer treatment (14), 28 children underwent pulmonary function assessment before and after HSCT. Again, LCI was a sensitive marker for cGvHD and was associated with persisting pulmonary symptoms, but LCI measured at HSCT was not predictive for the development of pulmonary cGvHD within one year after HSCT (14).

For spirometry indices, we identified only two studies that used the LLN to define abnormal spirometry as we did in our study and as recommended in the literature (26). In a Danish study of 94 leukemia survivors not exposed to pulmotoxic cancer treatment, with a median age at study of 16 years, abnormal FEV_1 , FVC, and FEV_1/FVC were observed in 8%, 15%, and 1% of survivors compared to 0%, 4%, and 4% in our standard risk group (22). In the other study of 41 Hodgkin and non-Hodgkin lymphoma survivors exposed to pulmotoxic cancer treatment, with a median age at study of 21 years, 27%, 27%, and 10% had abnormal FEV_1 , FVC, and FEV_1/FVC , which compares to 33%, 33%, and 7% in our high risk patients (7). One additional study also used the LLN with a lower cut-off (z score -2.00) (28). All other studies that included

abnormal spirometry indices used %-predicted to define abnormality and results are therefore not directly comparable to our findings (Table E4, online supplement).

As the first study to investigate N₂MBW in childhood cancer survivors, its strength derives from its standardized assessment of pulmonary function performed by a specialized, experienced pulmonary function laboratory. We included only high quality data after rigorous quality control, and technicians for pulmonary function assessment were blinded to the survivor's risk group. We collected detailed cancer treatment information for all patients.

One of the limitations of our study is that the study population was small and included a mix of different underlying diagnoses and pulmotoxic cancer treatments. However, the fact that we found some evidence for a benefit of N₂MBW in this heterogeneous group is encouraging and should stimulate further studies including larger numbers of participants. The small number of participants in our study did not allow to study treatment modalities separately, and also limits the interpretation of the differences found between HSCT and no-HSCT survivors. However, the fact that all HSCT survivors had abnormal S_{ACIN} parameters is worthwhile noticing and may suggest that total body irradiation and intensive conditioning regimens may have caused alveolar damage. Replication of our results and refined assessment in larger studies are needed before the place of N₂MBW in the clinical follow-up of childhood cancer survivors becomes clearer. Furthermore, we assessed pulmonary function only once in a cross-sectional fashion and did not have information on baseline pulmonary function before initiation of cancer treatment. Therefore, we cannot exclude preexisting preclinical pulmonary dysfunction. However, as survivors were asymptomatic and not aware of any pulmonary disease, this should not have substantially changed the results. Also the reference populations

used for establishing normal values for lung function tests might contain subjects with subclinical disease, that has resulted neither in symptoms nor in a diagnosis. Longitudinal studies assessing pulmonary function before, during, and after treatment will be useful to investigate whether abnormal N₂MBW indices predict future pulmonary morbidity and mortality in childhood cancer survivors. These studies should also measure diffusion capacity of the lungs for carbon monoxide (DLCO), which is another sensitive measure of early lung damage after chest radiation (28) and chemotherapy with bleomycin (29), but was not included in the current study. Further, there is no objective reference standard available, which represents early fibrotic changes in the lung, and against which we could assess performance of N₂MBW and spirometry. N₂MBW and spirometry are proxy measures for different anatomical abnormalities with N₂MBW measuring ventilation homogeneity of the whole lung and spirometry primarily measuring obstruction of the larger, proximal airways. Therefore, conclusions on the superiority of either measure cannot be drawn at this stage. Finally, follow-up time since cancer diagnosis was variable in our participants; however, we found no association between the length of follow-up time and pulmonary function parameters.

Pulmotoxic cancer treatment leads to inflammatory and fibrotic changes of the small airways. While busulfan, bleomycin, and nitrosoureas are currently recognized as pulmotoxic chemotherapeutic agents, cyclophosphamide (6), methotrexate (9), and cisplatin (5, 6) also have been implicated in pulmonary damage. This is consistent with our finding that a considerable proportion of the standard risk group (48%) had abnormal N₂MWB results that suggest some damage to the small airways.

Mortality due to pulmonary diseases following treatment for childhood cancer is particularly elevated (3). Yet early detection of pulmonary damage enables medical and lifestyle interventions that possibly improve pulmonary outcomes (30, 31). Our observation that spirometry was normal in standard risk patients stands in contrast to the pulmonary damage in half of this group that was suggested by N₂MBW. Because N₂MBW also is a tidal breathing test, the administration of which can be largely independent of the age and clinical condition of patients, N₂MBW can monitor pulmonary function during childhood.

We conclude that further study of childhood cancer survivors is needed, particularly longitudinal assessments, along with more sensitive surveillance of the pulmonary function of patients previously perceived as facing standard risk. Since N₂MBW identified more cases of pulmonary dysfunction than spirometry, we believe N₂MBW could be a complementary technique—for patients of all ages—for the screening of childhood cancer survivors for pulmonary damage.

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Table 1. Characteristics of childhood cancer survivors participating in the SURfit study and undergoing a pulmonary function assessment

	Total N=46 (100%)*	High risk[†] N=17 (37%)*	Standard risk[‡] N=29 (63%)*	p [§]	
Demographic characteristics					
Male sex	24 (52%)	9 (53%)	15 (52%)	0.936	
Age at study, median [IQR], years	30 [25–40]	31 [22–36]	28 [25–41]	0.559	
Clinical characteristics					
Age at diagnosis, median [IQR], years	10 [4–14]	12 [9–14]	6 [4–12]	0.016	
Time since diagnosis, median [IQR], years	20 [15–32]	18 [13–25]	24 [18–32]	0.083	
Weight at study, median [IQR], kg	68 [60–78]	64 [52–71]	74 [62–79]	0.029	
Height at study, median [IQR], cm	169 [163–177]	174 [161–179]	168 [163–174]	0.851	
Active smoking	10 (22%)	2 (12%)	8 (28%)	0.209	
ICCC-3 cancer diagnosis					
I Leukemia	25 (54%)	6 (35%)	19 (66%)	0.156	
II Lymphoma	11 (24%)	8 (47%)	3 (10%)		
III CNS tumor	2 (4%)	1 (6%)	1 (4%)		
IV Neuroblastoma	1 (2%)	0 (0%)	1 (4%)		
V Retinoblastoma	1 (2%)	0 (0%)	1 (4%)		
VIII Bone tumor	4 (9%)	2 (13%)	2 (7%)		
IX Soft tissue sarcoma	1 (2%)	0 (0%)	1 (3%)		
XIII LCH	1 (2%)	0 (0%)	1 (4%)		
History of relapse	2 (4%)	1 (12%)	1 (4%)		0.130
Any chemotherapy	44 (96%)	17 (100%)	27 (93%)		0.237
Any radiotherapy	23 (50%)	15 (88%)	8 (28%)	<0.001	
Chest radiation	15 (33%)	15 (88%)	0 (0%)	<0.001	
Median, [IQR], Gray	20 [12–35]	20 [12–35]	NA	NA	
Mediastinal/lung radiation	9 (20%)	9 (53%)	0 (0%)	<0.001	
Median, [IQR], Gray	27 [20–39]	27 [20–39]	NA	NA	
Cranio-spinal radiation	2 (4%)	2 (12%)	0 (0%)	0.059	
Median, [IQR], Gray	22 [20–23]	22 [20–23]	NA	NA	
Total body irradiation	4 (9%)	4 (24%)	0 (0%)	0.059	
Median, [IQR], Gray	12 [12–12]	12 [12–12]	NA	NA	
HSCT	5 (11%)	5 (29%)	0 (0%)	0.002	

Abbreviations: CNS, central nervous system; IQR, interquartile range; N, number; HSCT, hematopoietic stem cell transplantation; LCH, Langerhans cell histiocytosis; ICC-3, International Classification of Childhood Cancer, 3rd edition

* Column percentages are given

[†] High risk = pulmotoxic cancer treatment including busulfan, bleomycin, nitrosureas, chest radiation, thoracic surgery, HSCT

[‡] Standard risk = no pulmotoxic cancer treatment

[§] P-values comparing high risk and standard risk patients calculated from chi-squared tests for categorical variables and from t-tests for continuous variables

^{||} Including mediastinal/lung radiation, cranio-spinal radiation, and total body irradiation

Table 2. N₂MBW (LCI, FRC, S_{COND}, S_{ACIN}) and spirometry (FEV₁, FVC, FEV₁/FVC) indices in childhood cancer survivors, median age 30 years (N=46)

	Reference population*	Total N=46	High risk† N=17	Standard risk‡ N=29	P§
N₂MBW 					
LCI					
mean (SD)	6.94 (0.61)	7.77 (1.64)	8.22 (1.46)	7.52 (1.71)	0.195
z score, mean (SD)	NA	1.37 (2.69)	2.09 (2.39)	0.95 (2.81)	
FRC L					
mean (SD)	3.21 (0.81)	3.38 (1.10)	3.38 (1.13)	3.38 (1.10)	0.998
z score, mean (SD)	NA	0.21 (1.35)	0.21 (1.39)	0.20 (1.36)	
S_{COND}					
mean (SD)	0.028 (0.026)	0.018 (0.016)	0.017 (0.013)	0.018 (0.0170)	0.782
z score, mean (SD)	NA	-0.40 (0.60)	-0.44 (0.51)	-0.38 (0.65)	
S_{ACIN}					
mean (SD)	0.058 (0.028)	0.095 (0.090)	0.127 (0.092)	0.076 (0.078)	0.076
z score, mean (SD)	NA	1.34 (3.08)	2.45 (3.29)	0.65 (2.79)	
Spirometry ¶					
FEV₁					
mean (SD)	4.46	3.57 (0.83)	3.38 (1.00)	3.70 (0.69)	0.247
z score, mean (SD)	NA	-0.43 (1.26)	-0.94 (1.39)	-0.10 (1.07)	
FVC L					
mean (SD)	5.32	4.35 (1.12)	3.98 (1.10)	4.59 (1.09)	0.101
z score, mean (SD)	NA	-0.36 (1.58)	-1.14 (1.23)	0.15 (1.61)	
FEV₁/FVC					
mean (SD)	0.85	0.83 (0.09)	0.85 (0.08)	0.82 (0.10)	0.305
z score mean (SD)	NA	0.07 (1.24)	0.36 (1.14)	-0.12 (1.29)	

Abbreviations: FRC, functional residual capacity; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; HSCT, hematopoietic stem cell transplantation; LCI, lung clearance index; NA, not applicable; N₂MBW, nitrogen multiple-breath washout; N, number; SD, standard deviation; S_{ACIN}, acinar ventilation inhomogeneity index; S_{COND}, conductive ventilation inhomogeneity index

* Expected mean values from published reference populations: Husemann, Eur Respir J, 2014 (21) for N₂MBW; Quanjer, Eur Respir J, 2012 (22) for spirometry

† High risk = pulmotoxic cancer treatment including busulfan, bleomycin, nitrosureas, chest radiation, thoracic surgery, HSCT

‡ Standard risk = no pulmotoxic cancer treatment

§ P-values comparing high and standard risk patients calculated from t-tests

|| N₂MBW indices included after quality check; total survivors: 41 N₂MBW (41 LCI, 39 S_{ACIN}), high risk survivors: 15 N₂MBW (15 LCI, 15 S_{ACIN}), standard risk survivors: 26 N₂MBW (26 LCI, 24 S_{ACIN}); see also Figure E1

¶ Spirometry indices included after quality check; total survivors: 38 spirometry (38 FEV₁, 38 FVC), high risk survivors: 15 spirometry (15 FEV₁, 15 FVC), standard risk survivors: 23 spirometry (23 FEV₁, 23 FVC); see also Figure E1

Table 3. Prevalence of abnormal N₂MBW parameters (above the upper limit of normality) and spirometry parameters (below the lower limit of normality) in 46 childhood cancer survivors, median age 30 years, stratified into high and standard risk for pulmonary dysfunction

	Reference population*	Total N=46	High risk† N=17	Standard risk‡ N=29	P§
N₂MBW 					
LCI, ULN	5%	15/41 (37%)	9/15 (60%)	6/26 (23%)	0.018
FRC L, ULN	5%	6/41 (15%)	2/15 (13%)	4/26 (15%)	0.858
S _{COND} L ⁻¹ , ULN	5%	0/39 (0%)	0/14 (0%)	0/25 (0%)	NA
S _{ACIN} L ⁻¹ , ULN	5%	13/39 (33%)	8/15 (53%)	5/24 (21%)	0.036
Any abnormal N ₂ MBW value	NA	26/41 (63%)	12/15 (80%)	14/26 (54%)	0.094
Spirometry ¶					
FEV ₁ , LLN	5%	5/38 (13%)	5/15 (33%)	0/23 (0%)	0.003
FVC L, LLN	5%	6/38 (16%)	5/15 (33%)	1/23 (4%)	0.017
FEV ₁ /FVC, LLN	5%	2/38 (5%)	1/15 (7%)	1/23 (4%)	0.754
Any abnormal spirometry value	NA	7/38 (18%)	5/15 (33%)	2/23 (9%)	0.055

Abbreviations: LCI, lung clearance index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; FRC, functional residual capacity; LLN, lower limit of normality; N, number; NA, not applicable; N₂MBW, nitrogen multiple-breath washout; S_{ACIN}, acinar ventilation inhomogeneity index; S_{COND}, conductive ventilation inhomogeneity index; ULN, upper limit of normality

* Expected prevalence of abnormal pulmonary function parameters based on definitions of ULN = z score + 1.64 (for N₂MBW) and LLN = z score - 1.64 (for FEV₁ and FVC) and <0.7 for FEV₁/FEV

† High risk = pulmotoxic cancer treatment including busulfan, bleomycin, nitrosoureas, chest radiation, thoracic surgery, HSCT

‡Standard risk = no pulmotoxic cancer treatment

§ P-values comparing high and standard risk patients calculated from chi-squared tests

|| Included N₂MBW indices after quality check; total survivors: 41 N₂MBW (41 LCI, 39 S_{ACIN}), high risk survivors: 15 N₂MBW (15 LCI, 15 S_{ACIN}), standard risk survivors: 26 N₂MBW (26 LCI, 24 S_{ACIN})

¶ Included spirometry indices after quality check; total survivors: 38 spirometry (38 FEV₁, 38 FVC), high risk survivors: 15 spirometry (15 FEV₁, 15 FVC), standard risk survivors: 23 spirometry (23 FEV₁, 23 FVC)

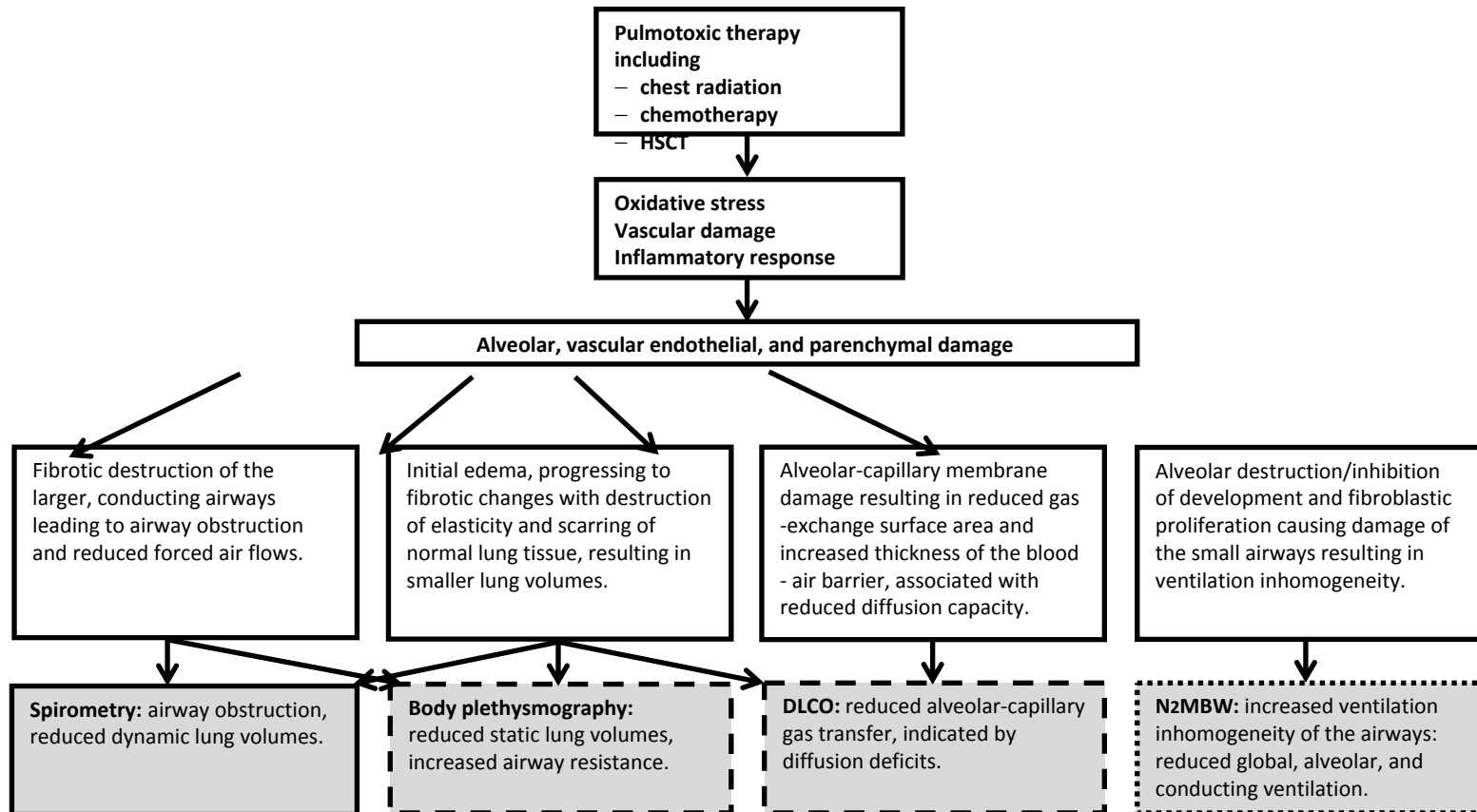
Figure Legends

Figure 1: Model of pathophysiological mechanisms underlying pulmotoxic effects of cancer therapy and relationship with lung function outcome measures. The white boxes describe mechanisms of cancer-treatment-related lung injury. Ionizing radiation from chest radiation, chemotherapy, and hematopoietic stem cell transplantation induce release of oxygen radicals, cause vascular damage, and promote inflammation in the lung. Persistent inflammation results in pathological changes in the alveolar, vascular endothelial, and parenchymal departments, which is associated with pathologic immune cell infiltration, capillary permeability, and pulmonary edema. The lung damage may be acute and reversible—presenting as pneumonitis, or chronic and irreversible—presenting as pulmonary fibrosis. The shaded boxes describe the outcome measures described in different types of lung function tests. The box framed with continuous lines describe lung function parameters assessed in previous studies and in this study; boxes framed in dashed line represents outcomes assessed in previous studies but not in this study; the box framed with a pointed line describes outcomes assessed only in this study. Abbreviations: DLCO, diffusing capacity of the lung for carbon monoxide; HSCT, hematopoietic stem cell transplantation; N₂MBW, nitrogen multiple-breath washout.

Figure 2. LCI in 46 adult childhood cancer survivors stratified into high risk – with and without HSCT – and standard risk for pulmonary dysfunction. Dashed blue line = ULN = 7.94 (21) Abbreviations: HSCT, hematopoietic stem cell transplantation; LCI, lung clearance index; ULN, upper limit of normality.

Figure 3. S_{ACIN} in 46 adult childhood cancer survivors stratified into high risk, with and without HSCT, and standard risk for pulmonary dysfunction. Dashed blue line = ULN = 0.10 (21)

Abbreviations: HSCT, hematopoietic stem cell transplantation; S_{ACIN} , acinar ventilation inhomogeneity index; ULN, upper limit of normality.



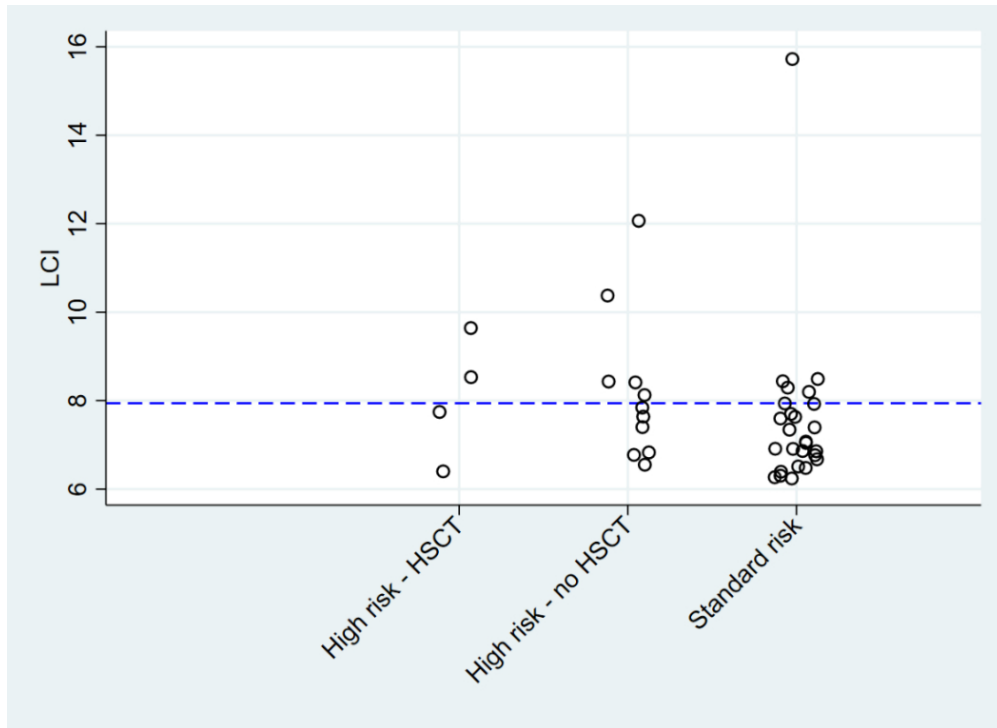


Figure 2. LCI in 46 adult childhood cancer survivors stratified into high risk – with and without HSCT – and standard risk for pulmonary dysfunction. Dashed blue line = ULN = 7.94 (21)
Abbreviations: HSCT, hematopoietic stem cell transplantation; LCI, lung clearance index; ULN, upper limit of normality

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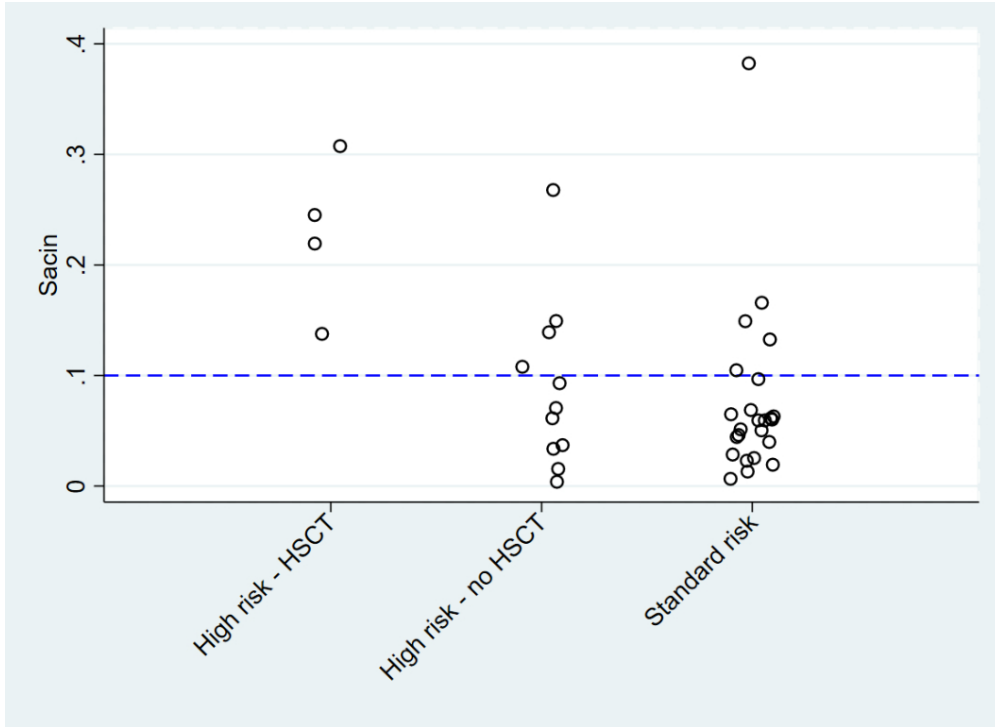


Figure 3. SACIN in 46 adult childhood cancer survivors stratified into high risk, with and without HSCT, and standard risk for pulmonary dysfunction. Dashed blue line = ULN = 0.10 (21)
Abbreviations: HSCT, hematopoietic stem cell transplantation; SACIN, acinar ventilation inhomogeneity index; ULN, upper limit of normality

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Online Supplement

Pulmonary dysfunction after treatment for childhood cancer: Comparing multiple-breath washout with spirometry

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Table E1. Characteristics of childhood cancer survivors participating in the SURfit study stratified into pulmonary assessment and no pulmonary function assessment

	All SURfit participants N=162 (100%)*	Pulmonary function assessed N=46 (28%)*	No pulmonary function assessed N=116 (72%)*	P†
Demographic characteristics				
Male sex	90 (56%)	24 (52%)	66 (57%)	0.585
Age at study, median [IQR], years	28 [23–37]	30 [25–40]	28 [23–28]	0.920
Clinical characteristics				
Age at diagnosis, median [IQR], years	7 [3–12]	10 [4–14]	6 [3–12]	0.017
Time since diagnosis, median [IQR], years	22 [16–29]	20 [15–32]	23 [16–29]	0.956
ICCC-3 cancer diagnosis				
I Leukemia	57 (35%)	25 (54%)	32 (28%)	0.011
II Lymphoma	34 (21%)	11 (24%)	23 (20%)	
III CNS tumor	18 (11%)	2 (4%)	16 (14%)	
IV-XIII other tumors	53 (33%)	8 (18%)	45 (38%)	
History of relapse	15 (9%)	3 (7%)	12 (10%)	0.451
Any chemotherapy	147 (91%)	44 (96%)	103 (89%)	0.299
Any radiotherapy	67 (41%)	23 (50%)	43 (37%)	0.124
HSCT	10 (6%)	5 (11%)	5 (4%)	0.118

Abbreviations: CNS, central nervous system; ICC-3, International Classification of Childhood Cancer, 3rd edition; IQR, interquartile range; N, number; HSCT, hematopoietic stem cell transplantation

* Column percentages are given

† P-values comparing survivors with and without pulmonary function assessment calculated from chi-squared tests for categorical variables and from t-tests for continuous variables

Table E2. Association between risk group and pulmonary function parameters (N₂-MBW and spirometry) in 46 adult childhood cancer survivors, median age 30 years at study. Results from univariable (Model 1) and multivariable linear regression adjusting for age, sex, weight, height and active smoking (Model 2)

	Model 1 Univariable linear regression	Model 2 Multivariable linear regression adjusted for age, sex, weight, height and smoking
	β coefficient* (95% CI), p-value	β coefficient* (95% CI), p-value
N2-MBW		
LCI, mean	0.695 (-0.371–1.760), p=0.195	1.110 (-0.188–2.398), p=0.092
FRC L, mean	0.001 (-0.727–0.729), p=0.998	-0.253 (-0.816–0.612), p=0.420
S _{COND} L ⁻¹ , mean	-0.002 (-0.012–0.009), p=0.782	0.004 (-0.009–0.016), p=0.548
S _{ACIN} L ⁻¹ , mean	0.050 (-0.005–0.106), p=0.076	0.036 (-0.032–0.103), p=0.292
Spirometry		
FEV ₁ , mean	-0.323 (-0.878–0.233), p=0.247	-0.239 (-0.704–0.226), p=0.303
FVC L, mean	-0.610 (-1.34–0.124), p=0.101	-0.778 (-1.400– -0.157), p=0.016
FEV ₁ /FVC, mean	0.032 (-0.030–0.094), p=0.305	0.066 (-0.005–0.137), p=0.066

Abbreviations: LCI, lung clearance index; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; FRC, functional residual capacity; LLN, lower limit of normal; N, number; NA, not applicable; N₂-MBW, nitrogen multiple-breath washout; S_{ACIN}, acinar ventilation inhomogeneity index; S_{COND}, conductive ventilation inhomogeneity index; ULN, upper limit of normal.

* The β coefficient is the degree of change in the N₂-MBW and spirometry parameters for high risk patients compared to low risk patients (reference).

Table E3. Characteristics and pulmonary function test results of the 17 high risk survivors undergoing pulmonary function testing

High risk survivors	Sex	Age, years	Childhood cancer diagnosis	HSCT	Chest radiation dose	Pulmotoxic chemotherapy	Abnormal LCI	Abnormal S _{ACIN}	Abnormal FEV ₁	Abnormal FVC	Any abnormality
1	F	21–25	Hodgkin	No	20 Gy	–	No	Yes	Yes	Yes	Yes
2	F	<21	Ewing sarcoma	No	45 Gy	–	Yes	Yes	Yes	Yes	Yes
3	F	36–40	Hodgkin	No	20 Gy	–	No	No	No	No	No
4	M	46–50	Hodgkin	No	27 Gy	–	Yes	Yes	No	No	Yes
5	F	21–25	Ewing	No	54 Gy	–	NA	NA	No	No	No
6	F	31–35	ALL	No	20 Gy	–	No	No	No	No	No
7	M	31–35	Hodgkin	No	20 Gy	–	Yes	Yes	No	No	Yes
8	F	21–25	Hodgkin	No	20 Gy	–	Yes	No	No	No	Yes
9	F	21–25	Hodgkin	No	35 Gy	–	Yes	No	NA	NA	Yes
10	M	36–40	Hodgkin	No	–	Bleomycin	No	No	No	No	No
11	M	46–50	T-NHL	No	39 Gy	–	Yes	No	Yes	Yes	Yes
12	M	26–30	Medulloblastoma	No	23 Gy	–	Yes	No	Yes	Yes	Yes
13	M	21–25	CML	Yes	12 Gy	–	No	Yes	NA	NA	Yes
14	F	31–35	CML	Yes	12 Gy	–	NA	NA	Yes	Yes	Yes
15	M	41–45	ALL	Yes	12 Gy	–	No	Yes	No	No	Yes
16	M	31–35	AML	Yes	12 Gy	–	Yes	Yes	No	No	Yes
17	M	21–25	MDS	Yes	–	Busulfan	Yes	Yes	No	No	Yes

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; F, female; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; HSCT, hematopoietic stem cell transplantation; Gy, gray; LCI, Lung clearance index; M, male; N, number; NA, not applicable/assessed; S_{ACIN}, acinar ventilation inhomogeneity index; MDS, myelodysplastic syndrome; T-NHL, T-non-Hodgkin lymphoma

Table E4. Studies on pulmonary function testing in childhood cancer survivors including the prevalence of individual abnormal spirometry indices

#	Publication First author Year Country	Sample size N	Survivor population Cancer diagnosis Age at study Pulmotoxic exposure	Cut-offs for abnormal indices			Prevalence of abnormal indices		
				FEV ₁	FVC	FEV ₁ /FVC	FEV ₁	FVC	FEV ₁ /FVC
1	De 2014 USA	80	Hodgkin, NHL, and GCT Not stated At least one pulmotoxic agent	<80% predicted	<80% predicted	<80% predicted	11%	9%	14%
2	De 2015 USA	49	All cancer diagnoses Median age 34 years At least one pulmotoxic agent	<80% predicted	<80% predicted	<80% predicted	29%	24%	14%
3	Denbo 2014 USA	21	Osteosarcoma Mean age 35 years At least one pulmotoxic agent	<80% predicted	<80% predicted	--	48%	40%	--
4	Green 2015 USA, Canada, Australia	260	Embryonal brain tumors Not stated At least one pulmotoxic exposure	<80% predicted	<80% predicted	--	29%	28%	--
5	Inaba 2010 USA	89	Leukemia with HSCT Not stated At least one pulmotoxic exposure	<80% predicted	<80% predicted	<80% predicted	36%	39%	23%
6	Jenney 1995 UK	69	Leukemia Median 15 years With and without pulmotoxic exposure	<80% predicted	<80% predicted	--	23%	20%	--
7	Leung 2007 USA	155	Leukemia with HSCT Median age 19 years At least one pulmotoxic exposure	--	--	<85% predicted	--	--	27%
8	Motosue 2012 USA	48	Solid tumors Adolescent and adult At least one pulmotoxic agent	<80% predicted	<80% predicted	<80% predicted	65%	58%	23%

9	Mulder 2011 The Netherlands	193	All cancer diagnoses Median age 27 years At least one pulmotoxic exposure	<80% predicted	<75% predicted	<70% predicted	21%	18%	3%
10	Nysom 1998 Denmark	41	Hodgkin and NHL Median age 21 years At least one pulmotoxic exposure	LLN z score - 1.64	LLN z score - 1.64	LLN= z score - 1.64	27%	27%	10%
11	Nysom 1998 Denmark	94	Leukemia Median age 16 years No pulmotoxic exposure	LLN z score - 1.64	LLN z score - 1.64	LLN z score - 1.64	8%	15%	1%
12	Record 2012 USA	143	All cancer diagnoses Mean age 14 years At least one pulmotoxic agent	<80%	<80%	<80%	26%	25%	5%
13	Weiner 2006 USA	30	Solid tumors Median age 12 years At least one pulmotoxic agent	LLN z score - 2.00	LLN z score - 2.00	--	50%	53%	--

Abbreviations: CCS, childhood cancer survivors; GCT, germ cell tumor; HSCT, hematopoietic stem cell transplantation; LLN, lower limit of normality; N, number; NHL, non-Hodgkin lymphoma

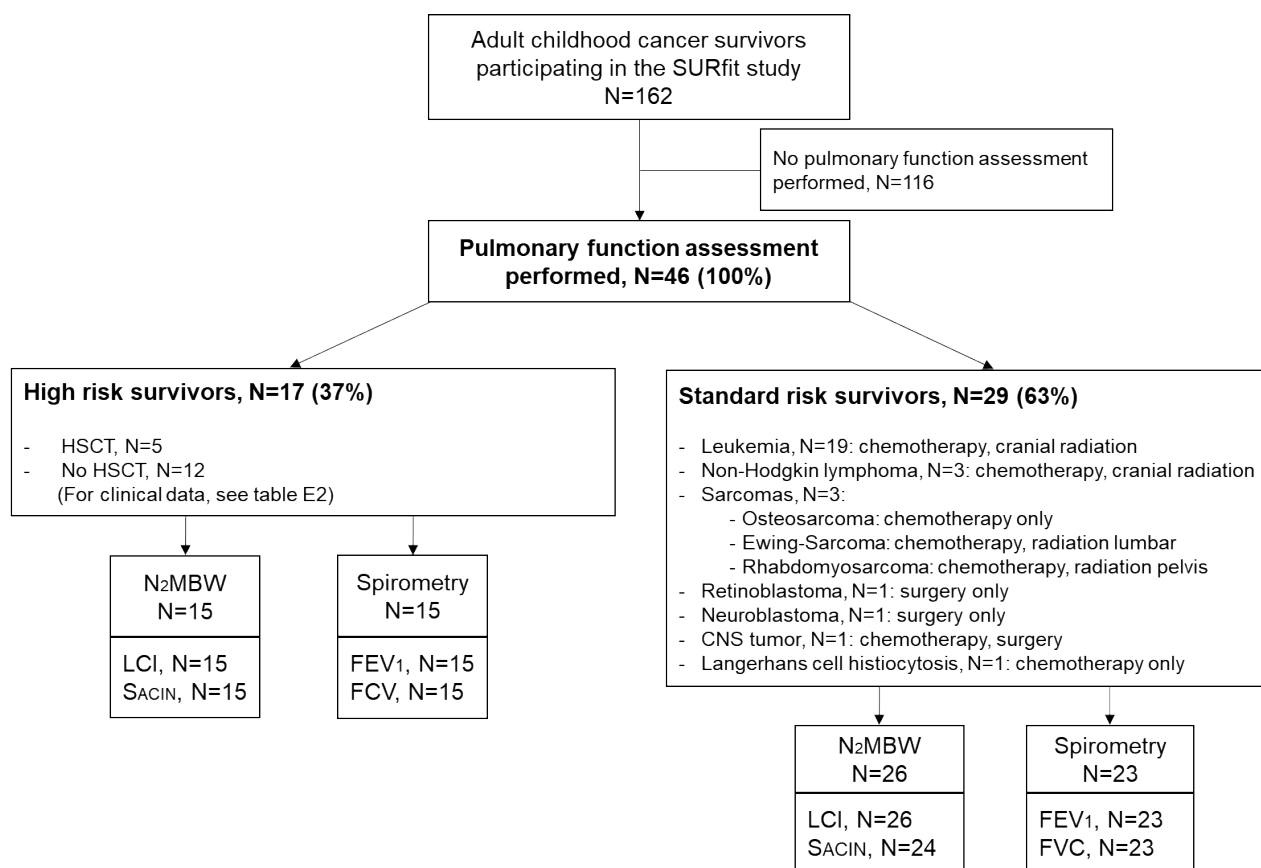


Figure E1. Population tree of study participants of the SURfit study who were recruited for a lung function assessment using N₂MBW and spirometry

Abbreviations: CNS, central nervous system; LCI, lung clearance index; N, numbers; HSCT, hematopoietic stem cell transplantation; N₂MBW, nitrogen multiple-breath washout; S_{ACIN}, acinar ventilation inhomogeneity index