Published in final edited form as:

Cancer. 2016 December 1; 122(23): 3687–3696. doi:10.1002/cncr.30200.

Risk and Impact of Pulmonary Complications in Survivors of Childhood Cancer: A Report from the Childhood Cancer Survivor Study (CCSS)

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Abstract

Background—Pulmonary complications after cancer therapy are varied. We describe pulmonary outcomes among childhood cancer survivors and evaluate their impact on daily activities.

Methods—The incidence of pulmonary outcomes (asthma, chronic cough, emphysema, lung fibrosis, oxygen need, recurrent pneumonia) reported among 5-year cancer survivors (n=14,316) and death from pulmonary causes among all eligible survivors (n=20,690) in the Childhood Cancer Survivor Study (CCSS) were compared to sibling controls (n=4,027) using cumulative incidence, standardized mortality ratio (SMR), and piecewise exponential models. Logistic regression with random effects was used to estimate odds ratios (ORs) and 95% confidence intervals (CI) of activity limitations with pulmonary complications.

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Authors indicate no conflicts of interest

Contributions:

Concept and design: ACD, DAM, LLR, GTA, KCO

Funding/provision of study materials/patients: LLR, GTA

Data analysis/interpretation: All authors

Manuscript writing/revising/approval: All authors

Results—By age 45 years the cumulative incidence of any pulmonary condition was 29.6% (CI 29.1–30.0) among cancer survivors and 26.5% (CI 24.9–28.0) for siblings. Fewer survivors reported ever smoking (23.6 vs. 36.4%, $p<0.001$), but survivors were more likely to report chronic cough (rate ratio [RR] 1.6 CI 1.4–1.9), oxygen need (RR 1.8 CI 1.5–2.2), lung fibrosis (RR 3.5 CI 2.3–5.4), and recurrent pneumonia (RR 2.0 CI 1.4–3.0). The SMR for death from pulmonary causes was 5.9 (CI 4.2–8.1) and associated with platinum exposure and lung radiation ($p<0.01$). Impact of chronic cough on daily activities for survivors (OR 2.7 relative to survivors without chronic cough) was greater than for siblings (OR 2.0, $p=0.04$).

Conclusion—Pulmonary complications are substantial among adult survivors of childhood cancer and can impact daily activities.

Précis

Pulmonary complications are substantial among adult survivors of childhood cancer and can impact daily activities.

Keywords

Survivorship; Pulmonary Toxicity; Childhood Cancer; Late-Effects; Cancer treatment

Introduction

Cooperative group trials, multi-modal and risk-based therapies, and pharmacologic advances have contributed to consistent survival improvements for children diagnosed with a malignancy. Overall 5-year survival rates now exceed 80%, and it is estimated there are more than 420,000 survivors of childhood cancer alive in the United States.¹ With these improvements, research efforts have increasingly focused on late sequelae of cancer therapy in an effort to better characterize and understand risks to long-term health and need for appropriate screening and counseling.

Despite improved survival rates, late mortality for childhood cancer survivors exceeds the expected rate estimated from the age-, sex-matched United States population.² Leading causes of death are subsequent malignant neoplasms (SMN) (standardized mortality ratio [SMR] 15.2) followed by pulmonary (SMR 8.8), and cardiovascular (SMR 7.0) events. Late pulmonary toxicity following chemotherapy and/or radiation therapy has been reported by many investigators and appears highest among survivors of Hodgkin lymphoma, leukemia, rhabdomyosarcoma, and hematopoietic stem cell transplant (HSCT).^{3–6} Perhaps more important is the continued increase in adverse pulmonary outcomes with time. Cumulative incidence for lung fibrosis, chronic cough, and exercise-induced dyspnea continues to increase up to 25 years from diagnosis among survivors treated with chemotherapy or radiation,⁷ while the combination is associated with the highest risk.^{8, 9} Lack of any plateau suggests the need for follow-up with advancing age and time from diagnosis.

Understanding specific long-term risks to pulmonary health for survivors of childhood cancer will help refine guidelines for appropriate screening and surveillance, promote health counseling, and, hopefully, contribute to design and testing of targeted interventions to decrease pulmonary morbidity and mortality for future cancer survivors. This study seeks to

expand upon our understanding of the occurrence of and risk factors for adverse pulmonary outcomes among aging survivors of childhood cancer, as well as assess associations with daily physical activity.

Methods

Population

The Childhood Cancer Survivor Study (CCSS), a multi-institutional retrospective cohort study, has longitudinal follow-up of individuals who survived at least 5 years after diagnosis of leukemia, central nervous system (CNS) malignancy, Hodgkin or non-Hodgkin lymphoma, kidney tumor, neuroblastoma, soft-tissue sarcoma, or bone tumors, diagnosed before age 21 years at one of 26 collaborating institutions between January 1, 1970 and December 31, 1986. Participants completed a baseline survey between 1994–98 that included demographic information and medical, family, and social histories. A surrogate (parent, spouse, or next of kin) completed the baseline survey for survivors who died more than 5 years after diagnosis, were under age 18 years, or unable to complete the survey. Questions concerning pulmonary conditions were asked on the baseline and two subsequent follow-up surveys, follow-up 2 (FU2) and follow-up 4 (FU4) (conducted in 2000 and 2007, respectively), but not on follow-up 1 or follow-up 3. Participants must have completed at least one relevant survey to be included in this analysis. Treatment data were abstracted from medical records for survivors who authorized release. The dose for lung radiation was an average absorbed dose calculated to 400 points in each lung.¹⁰ The dose used for analysis was the greater of the right or the left lung. The CCSS study has been previously described,¹¹ approved by the human subjects review committees at each institution, and all participants and/or guardians provided informed consent. Surveys can be viewed at <http://ccss.stjude.org>.

We identified 20,690 five-year cancer survivors, of whom 14,359 (69%) completed baseline, FU2, and/or FU 4 questionnaires. Survivors reporting a second cancer prior to cohort entry (n=43) were excluded, leaving 14,316 in this analysis (Supplemental Figure 1). A random sample of survivors were asked to nominate their nearest aged sibling for participation in a comparison group, resulting in 4,027 siblings who completed baseline, FU2, and/or FU4 questionnaires.

Pulmonary Outcomes

Participants completed multi-item questionnaires, which included earliest onset age of a pulmonary health condition: asthma, chronic cough, emphysema, lung fibrosis, oxygen need, and recurrent pneumonia (3 or more episodes in the past 2 years). Second malignant neoplasms (SMN) were confirmed by central review of pathology reports. Congestive heart failure (CHF) was assessed in surveys and graded per Common Terminology Criteria for Adverse Events (version 4.03) with grades 3–4 considered positive for CHF.¹² All patients eligible for participation (n=20,690) were included in a search for matching death records using the National Death Index through 2007. Underlying and multiple causes of death for deceased subjects, using the International Classification of Disease – 9th and 10th Revisions,

were provided and pulmonary deaths as the underlying cause (ICD 9: 460–519, ICD 10: J00-J99) identified.

Physical activity limitations were scored as previously described¹³ from baseline and FU4 surveys. A series of six questions asked about how long current health status limited performance of particular activities during the past 2 years. Activities included vigorous ones such as lifting heavy objects or running, moderate activities such as carrying groceries or climbing a few flights of stairs, and light activities such as stooping, walking 1 block, or bathing. Scores were assigned based on duration of limitation, creating a continuous variable. Subjects were classified as having physical activity limitations if their scores were at or below the 10th percentile of the sibling group's overall score.

Statistical Analysis

Characteristics of survivors and siblings were tabulated and compared between them through bootstrapping of families to account for potential within-family correlation.¹⁴ The SMR was calculated using age-, sex-, and calendar year-specific U.S. mortality rates among all eligible survivors (n=20,690). Cumulative incidence of pulmonary conditions were calculated for survivors and siblings with SMN, late recurrence, HSCT, or death for survivors and death for siblings as competing risk events. Multivariable piecewise exponential models were used to compare incidence rates of each pulmonary outcome between survivors and siblings, adjusting for sex, race, and time-dependent variables of attained age, smoking status, body mass index (BMI), and incidence of CHF. Survivors were considered to be at risk for developing each pulmonary condition starting from CCSS cohort entry (i.e. 5 years after cancer diagnosis); the siblings' at-risk period started on the date when his/her index case (survivor) became a five-year survivor. The at-risk period ended at the earliest of: developing the pulmonary condition of interest, SMN, late recurrence, receiving HSCT, death, or completion date of the last questionnaire. Modification of models by Generalized Estimating Equation (GEE) was used to account for potential correlation of developing each pulmonary condition of interest within family (between a survivor and his/her sibling).¹⁵ Absolute excess risk (AER) per 10,000 person years was calculated by subtracting siblings adjusted incidence rates from survivors adjusted incidence rates.

Associations between treatment exposures and pulmonary conditions were assessed by multivariable piecewise exponential regression analysis, adjusting for sex, race, cancer diagnosis, attained age, years since cancer diagnosis, smoking status, BMI, and incidence of CHF. A variable selection for treatment exposures was performed retaining variables with a p-value < 0.2 on univariate analysis in final models.

Associations of having developed pulmonary conditions with physical activity limitations were evaluated longitudinally and compared between survivors and siblings. CNS tumor survivors were excluded from this analysis because of their previously described physical activity limitations.¹⁶ To compare differences between survivors and siblings, logistic regression analysis with random effects¹⁷ was performed, adjusting for sex, race, attained age, smoking, HSCT, amputation, paralysis, and CHF. Two sources of correlation across multiple physical limitation measures at different survey times were accounted for by two

random effects: one for within-family correlation between a survivor and his/her sibling and the other for within-person across-survey repeated measurements.

A multiple imputation method¹⁸ was used for those who reported a condition without onset age. Multiple possible ages were imputed for each missing age for survivors and siblings separately, using all variables from the analyses above (Supplemental Table 1). Ten multiply-imputed datasets were generated. By applying the same analysis to each of these datasets, 10 sets of results were summarized by the standard method for multiple-imputation-based inference.¹⁹

Results

Population

Characteristics of survivors and siblings are shown in Table 1. Median age at diagnosis was 7 years (range: 0–21) and 32 years (6–59) at evaluation, with median time from diagnosis of 25 years (5–39). Compared with siblings, survivors were more likely to be male, black, and Hispanic. Survivors were slightly younger and more likely to report a history of CHF, but less likely to be overweight/obese or have ever smoked at baseline survey.

Pulmonary Conditions

The frequency of pulmonary conditions, incidence rates, cumulative incidence, and AER are shown in Table 2. Incidence rates for survivors ranged from 0.2 for emphysema to 4.9 for chronic cough per 1,000 person-years. At age 45 years the cumulative incidence for reporting any pulmonary condition was 29.6% (95% CI 29.1%–30.0%) in survivors and 26.5% (95% CI 24.9%–28.0%) in siblings (Figure 1a–g). Compared to siblings, AERs were elevated for chronic cough, oxygen need, lung fibrosis, and recurrent pneumonia among survivors.

Compared to siblings, survivors had higher rate ratios (RR) for developing new onset chronic cough (RR 1.6 95% CI 1.4–1.9), oxygen need (RR 1.8 95% CI 1.5–2.2), lung fibrosis (RR 3.5 95% CI 2.3–5.4), and recurrent pneumonia (RR 2.0 95% CI 1.4–3.0) (Table 2). Rate ratios for chronic cough, oxygen need, and lung fibrosis remained elevated up to 25 years post diagnosis but declined for recurrent pneumonia with longer follow-up (Supplemental Table 2).

Exposures Associated with Pulmonary Outcomes

Associations between treatment exposures and adverse pulmonary outcomes are shown in Table 3. The risk of asthma was increased among survivors exposed to asparaginase. Chronic cough was significantly associated with chest wall or lung surgery, anthracyclines, hydroxyurea, and lung radiation 15 Gy. Emphysema was associated with lomustine (CCNU). HSCT, chest wall or lung surgery, and lung radiation 10 Gy were associated with oxygen need. Lung fibrosis was associated with previous chest wall or lung surgery, asparaginase, platinum-based agents, and lung radiation 10 Gy. The risk of recurrent pneumonia was increased by lung radiation 15 Gy. No significant interactions were identified between chemotherapy and radiation exposures.

Limitations in Daily Activities

Table 4 shows the effect of each pulmonary condition on daily activities for survivors and siblings. Survivors with each pulmonary condition were more likely to have activity limitations than survivors without these conditions. With the exception of recurrent pneumonia, siblings also reported activity limitations across all pulmonary conditions compared to those siblings without these conditions. However, the frequency of limitations was higher among survivors with chronic cough compared to siblings with chronic cough ($p=0.04$). While not statistically significant, the frequency also tended to be higher for survivors needing oxygen ($p=0.09$) and those with recurrent pneumonia ($p=0.08$), compared to siblings with these conditions.

Pulmonary Mortality

Cumulative incidence of death due to a pulmonary cause rises steadily with increasing time from diagnosis, exceeding 0.5% by 35 years after diagnosis (Figure 2). There were 138 reported pulmonary deaths (SMR 5.9, 95% CI 4.2–8.1). Significant associations were identified with exposure to platinum-based agents (RR 6.9 95% CI 1.8–27.3), and higher lung radiation doses (RR 4.4 95% CI 1.0–18.5, for 10 to <15; RR 7.7 95% CI 2.0–29.1, for 15 to <20 Gy; RR 5.2 95% CI 1.2–22.3, for 20 to <25 Gy; RR 15.7 95% CI 3.7–65.5, for 25 Gy; $p_{\text{trend}} < 0.01$).

Discussion

Late complications of cancer therapy affecting the pulmonary system are heterogeneous and range from self-limited events to more severe conditions impacting daily activity, contributing to late morbidity, and increasing the risk of death. Following the largest cohort of adult survivors of childhood cancer for a median of 25 years, we identified a variety of pulmonary outcomes. The rate of chronic cough, oxygen need, lung fibrosis, and recurrent pneumonia remained elevated many years from diagnosis. Additionally, we investigated the impact these complications have upon activities of daily living. Survivors with chronic cough, and potentially oxygen need and recurrent pneumonia, were more likely to report activity limitations than siblings with these same conditions.

Some respiratory outcomes such as asthma are particularly common, and, therefore, highly prevalent among survivors and siblings. These findings are consistent with the initial report of pulmonary outcomes in the CCSS cohort.⁷ However, using data from across three surveys, we found the rate of newly diagnosed chronic cough, oxygen need, lung fibrosis, and recurrent pneumonia continued to occur many years following diagnosis. Chronic cough, one of the most common respiratory complaints in the general population, accounts for 38% of outpatient pulmonary clinic visits, and can lead to feelings of self-consciousness, social isolation, musculoskeletal pain, and chronic hoarseness.²⁰ Lung fibrosis can range from an asymptomatic finding to a progressive, irreversible, fatal process, with median survival of 2–5 years following diagnosis.²¹ Recurrent pneumonia, one of the most common reasons for physician visits and hospitalizations, occurs in 9–12% of the general population and has been associated with 4–10% mortality.²² Impaired functional status and immunosuppression have been significantly associated with recurrent pneumonia,

particularly among aging adults. However, many of these same co-morbidities have also been identified among younger adult survivors of childhood cancer and the contribution to adverse pulmonary outcomes has yet to be fully investigated.^{16, 23}

Pulmonary tissue is particularly sensitive to cancer treatment both acutely and long-term. Radiation and chemotherapy-induced pneumonitis can progress to lung fibrosis, while thoracic surgery can leave long-term anatomical abnormalities effecting respiratory physiology.^{8, 9} Our study confirms many of these associations, however, associations with chemotherapy appeared less prominent. On multivariable analysis, many of the classic alkylating agents, such as bleomycin, busulfan, and BCNU, showed no association with the pulmonary outcomes studied. This is not unlike recent studies that performed pulmonary function testing on childhood cancer survivors. Among 220 survivors treated with bleomycin, pulmonary radiation, or pulmonary surgery, Mulder et al. identified restrictive lung disease in those treated with radiation only (OR 6.99 95% CI 2.27–21.54), bleomycin and radiation (OR 9.41 95% CI 1.71–51.86), and radiation with surgery (OR 33.44 95% CI 7.81–143.09) compared to those treated with bleomycin only.⁸ Similarly, Armenian and colleagues in a series of 155 survivors found restrictive physiology associated with chest radiation >20 Gy (OR 5.6, 95% CI 1.5–21.0) but no significant associations with chemotherapy exposures.²⁴ Lung radiation and surgery appear to have the most significant impact upon the lung.

A number of unique associations with chemotherapy were identified. A newer finding was the association of asparaginase with asthma and lung fibrosis. Hypersensitivity reactions to asparaginase are common, usually acute, IgE mediated, and range from localized irritation to severe anaphylaxis.²⁵ Potentially immune-mediated pulmonary injury may occur following exposure initiating a chronic inflammatory state. Platinum agents were also associated with lung fibrosis. While a mechanism is not immediately clear, this association was also identified by Mertens et al.⁷ Inhaled heavy metals are known to be pulmonary toxic and, interestingly, these agents are associated with hypersensitivity reactions. A chance finding cannot be ruled out, but the persistence of this association raises important questions for future investigation. Anthracyclines and hydroxyurea were associated with chronic cough, independent of CHF. Rare cases of hydroxyurea-induced pneumonitis have been reported²⁶, but these associations, also, need further investigation.

Studies examining activity among childhood cancer survivors have largely focused on physical exercise and less on accomplishing routine daily tasks.²⁷ Ness and colleagues were among the first to report limitations in daily function in childhood cancer survivors (19.6% of the CCSS cohort, RR 1.8 95% CI 1.7–2.0).¹³ Our analysis is the first time associations have been made between specific adverse pulmonary outcomes and daily function. Pulmonary conditions were associated with reporting activity limitations for both cancer survivors and siblings. However, the impact of chronic cough was more significant among childhood cancer survivors than siblings, suggesting a greater influence and limitation on daily function among cancer survivors.

Using the CCSS cohort, we were able to assess a large population of childhood cancer survivors followed for late pulmonary outcomes. While the size of the cohort permits

investigation into an array of exposures not possible in smaller, single disease studies, the results should be interpreted within the limitations of the study design. Outcomes are self-reported and not formally validated. Validation of outcomes in the CCSS has been attempted, and while some are easier (e.g. birth of a child) than others, confirmation is challenging in the current health care environment.²⁸ Respiratory conditions, such as lung fibrosis or emphysema, can be particularly complex requiring specialized providers and a variety of diagnostic studies. Lacking verification, we chose to retain what individual survivors directly reported. While informative, caution is advised when interpreting the results and applying them to particular clinical scenarios. Another limitation is overlap among outcomes, such as chronic cough or oxygen need in patients with emphysema and/or lung fibrosis. Future prospective studies that follow self-reported pulmonary events, measure changes in lung function, and examine potential biomarkers could aid in earlier detection of these outcomes.

Survivors of childhood cancer are at increased risk for late pulmonary-related complications and mortality with increasing incidence over time. Often considered asymptomatic, late pulmonary toxicity may limit activities of daily living with potential impact on overall quality of life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported by the National Cancer Institute (CA55727, PI:G.T. Armstrong), Cancer Center Support (CORE) grant to St. Jude Children's Research Hospital (CA21765, PI:C. Roberts), and the American Lebanese-Syrian Associated Charities (ALSAC).

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Figure 1.
Cumulative Incidence of Pulmonary Conditions
Solid Line = Survivors; Dashed Line = Siblings

Figure 2.
Cumulative Incidence of Pulmonary Deaths

Table 1**Demographic and Treatment Characteristics of the Study Population**

Characteristic *	Survivors (n=14,316)	Siblings (n=4,027)	p-value
Sex			<0.001
Male	7693 (53.7%)	1940 (48.1%)	
Female	6623 (46.3%)	2087 (51.9%)	
Race/Ethnicity			<0.001
White, Non-Hispanic	12360 (86.3%)	3513 (87.2%)	
Black, Non-Hispanic	692 (4.8%)	112 (2.8%)	
Hispanic	750 (5.2%)	148 (3.7%)	
Other	514 (3.6%)	254 (6.3%)	
Age at last questionnaire			<0.001
<19 years	1233 (8.6%)	227 (5.6%)	
19–29 years	4633 (32.4%)	1175 (29.2%)	
30–39 years	5281 (36.9%)	1394 (34.6%)	
40–49 years	2799 (19.6%)	977 (24.3%)	
50 years	370 (2.6%)	253 (6.3%)	
Smoker †			<0.001
Current	2049 (14.3%)	856 (21.3%)	
Former	1337 (9.3%)	607 (15.1%)	
Never	10385 (72.5%)	2504 (62.2%)	
Missing	545 (3.8%)	60 (1.5%)	
Body mass index (BMI) ‡			<0.001
<18.5 kg/m2	1690 (11.8%)	314 (7.8%)	
18.5–24 kg/m2	7459 (52.1%)	2140 (53.1%)	
25–29 kg/m2	3168 (22.1%)	1009 (25.1%)	
30 kg/m2	1544 (10.8%)	535 (13.3%)	
Missing	455 (3.2%)	29 (0.7%)	
History of congestive heart failure			<0.001
Yes	358 (2.5%)	12 (0.3%)	
No	13958 (97.5%)	4015 (99.7%)	
Cancer Diagnosis			
Acute Leukemia	4817 (33.6%)		
Central Nervous System Tumors	1874 (13.1%)		
Hodgkin Lymphoma	1920 (13.4%)		
Non-Hodgkin Lymphoma	1074 (7.5%)		
Kidney Tumors	1254 (8.8%)		
Neuroblastoma	952 (6.6%)		

Characteristic *	Survivors (n=14,316)	Siblings (n=4,027)	p-value
Soft Tissue Sarcoma	1242 (8.7%)		
Ewing Sarcoma	402 (2.8%)		
Bone Tumors	781 (5.5%)		
Age at diagnosis			
<5 years	5739 (40.1%)		
5–9 years	3196 (22.3%)		
10–14 years	2897 (20.2%)		
15 years	2484 (17.4%)		
Survival Time			
5–9 years	877 (6.1%)		
10–19 years	2497 (17.4%)		
20–29 years	7732 (54.0%)		
30 years	3210 (22.4%)		
Treatment Exposures *			
Hematopoietic stem cell transplant	430 (3.0%)		
Chest Wall Surgery	1058 (7.4%)		
Lung Surgery	541 (3.8%)		
Chemotherapy			
Vinca Alkaloids	9152 (63.9%)		
Steroids	6187 (43.2%)		
Alkylators	6517 (45.5%)		
Cyclophosphamide	5491 (38.4%)		
Ifosfamide	97 (0.7%)		
BCNU	474 (3.3%)		
CCNU	446 (3.1%)		
Busulfan	27 (0.2%)		
Antimetabolites	5840 (40.8%)		
Methotrexate	5264 (36.8%)		
6-Mercaptopurine	3953 (27.6%)		
6-Thioguanine	1169 (8.2%)		
Cytarabine	2324 (16.2%)		
Asparaginase	3928 (30.9%)		
Anthracyclines	3928 (27.4%)		
Actinomycin	4947 (34.6%)		
Platinum-based agents	2499 (17.5%)		
Epipodophyllotoxins	661 (4.6%)		
Hydroxyurea	983 (6.9%)		
Bleomycin	510 (3.6%)		
Lung Irradiation#			
None	4122 (28.8%)		

Characteristic [*]	Survivors (n=14,316)	Siblings (n=4,027)	p-value
>0 to <5 Gy	5397 (37.7%)		
5 to <10 Gy	663 (4.6%)		
10 to <15 Gy	683 (4.8%)		
15 to <20 Gy	659 (4.6%)		
20 to <25 Gy	528 (3.7%)		
25 Gy	185 (1.3%)		

^{*} Percentages provided from among survivors for whom data are available. Treatment exposures are not exclusive.

[†] Reported at baseline.

[#] Lung radiation dose is the average dose to the lung that received the greater radiation exposure.

Table 2

Frequency, Incidence Rate (IR), Absolute Excess Risk (AER), Cumulative Incidence (CI), and Rate Ratios (RR) of Pulmonary Conditions

Pulmonary Condition	Number of Events		IR per 1,000 Person Years for Survivors (95% CI)	AER per 10,000 Person Years for Survivors (95% CI)	CI at 45 Years for Survivors (95% CI)	RR in Survivors vs. Siblings (95% CI) [#]
	Survivors N (%)	Siblings N (%)				
Asthma	1024 (7.6)	332 (9.3)	4.6 (4.3–4.9)	0.5 (–3.6–5.14)	12.2% (11.9–12.6%)	1.0 (0.9–1.2)
Chronic cough	1115 (8.1)	244 (6.5)	4.9 (4.6–5.3)	14.9 (9.6–21.1) [*]	14.9% (14.4–15.3%)	1.6 (1.4–1.9) [*]
Emphysema	49 (0.3)	9 (0.2)	0.2 (0.1–0.3)	0.5 (0.0–1.3)	0.6% (0.4–0.8%)	2.2 (0.9–5.0)
Oxygen Need	801 (5.9)	143 (3.9)	3.5 (3.2–3.7)	14.8 (9.1–21.6) [*]	11.6% (11.3–12.0%)	1.8 (1.5–2.2) [*]
Lung fibrosis	271 (1.9)	26 (0.7)	1.1 (1.0–1.3)	6.7 (3.4–11.8) [*]	5.4% (5.1–5.7%)	3.5 (2.3–5.4) [*]
Recurrent pneumonia	239 (1.7)	38 (1.0)	1.0 (0.9–1.1)	3.6 (1.4–6.9) [*]	4.0% (3.7–4.2%)	2.1 (1.4–3.1) [*]

[#]AER and RR were adjusted for sex, race, and time dependent variables of attained age, smoking status, BMI, and CHF;

^{*}p<0.05

Table 3
Rate ratio (RR) for Treatment Factors by Pulmonary Conditions in Multivariable Analysis

Treatment Factor	RR with 95% Confidence Interval (CI) [#]					
	Asthma	Chronic Cough	Emphysema	Oxygen Need	Lung Fibrosis	Recurrent Pneumonia
Hematopoietic stem cell transplant	1.2 (0.8–1.8)	1.5 (1.0–2.2)	2.6 (0.7–9.0)	1.8 (1.1–2.9) *	2.1 (0.9–4.9)	1.7 (0.8–3.7)
Surgery						
Chest Wall/Lung Surgery	1.2 (0.9–1.5)	1.4 (1.1–1.7) *		1.5 (1.2–1.9) *	1.5 (1.0–2.2) *	1.2 (0.8–2.0)
Spine Surgery				2.1 (0.7–6.4)		
Chemotherapy						
Vinca Alkaloids		1.0 (0.8–1.3)				
Steroids	0.8 (0.6–1.1)		1.5 (0.5–4.4)	1.0 (0.7–1.3)		
Alkylators	0.9 (0.7–1.1)	1.1 (0.9–1.3)	3.4 (1.0–11.2) *	1.1 (0.9–1.4)	1.1 (0.8–1.5)	1.1 (0.8–1.7)
CCNU						
Antimetabolites		1.1 (0.8–1.5)		1.3 (0.9–1.9)	1.2 (0.6–2.3)	
Methotrexate						
Mercaptopurine	0.8 (0.5–1.1)					1.3 (0.7–2.6)
Thioguanine	1.0 (0.7–1.4)					
Asparaginase	1.5 (1.1–2.2) *	1.0 (0.7–1.5)		1.4 (0.9–2.2)	2.3 (1.0–5.0) *	
Anthracyclines	1.2 (1.0–1.4)	1.2 (1.0–1.5) *	1.8 (0.8–3.9)	1.2 (1.0–1.5)		1.3 (0.8–1.9)
Actinomycin		1.1 (0.8–1.5)		1.1 (0.7–1.6)		
Platinum-based agents		1.1 (0.7–1.5)		1.3 (0.9–2.0)	2.1 (1.0–4.4) *	
Epipodophyllotoxins		1.2 (0.9–1.7)		1.0 (0.7–1.5)		1.3 (0.7–2.3)
Hydroxyurea		1.5 (1.0–2.2) *				
Bleomycin				1.2 (0.8–1.8)		
Radiation						
Spine Irradiation		1.0 (0.7–1.4)		1.1 (0.7–1.6)	1.0 (0.4–2.4)	1.3 (0.6–2.6)
Lung Irradiation **						
>0 to <5Gy	0.9 (0.7–1.0)	0.9 (0.7–1.0)		1.0 (0.8–1.2)	1.0 (0.6–1.7)	1.0 (0.6–1.5)
5 to <10 Gy	1.2 (0.9–1.7)	1.2 (0.9–1.7)		1.3 (0.9–1.9)	1.0 (0.4–2.7)	1.0 (0.4–2.3)

Treatment Factor	RR with 95% Confidence Interval (CI) [#]				
	Asthma	Chronic Cough	Emphysema	Oxygen Need	Lung Fibrosis
10 to <15 Gy	0.9 (0.7–1.3)	1.2 (0.9–1.6)		1.6 (1.1–2.3) *	3.8 (2.1–7.0) *
15 to <20 Gy	0.7 (0.5–1.1)	1.6 (1.2–2.2) *		1.9 (1.3–2.8) *	6.2 (3.3–11.4) *
20 to <25 Gy	1.3 (0.9–2.0)	1.9 (1.4–2.8) *		2.5 (1.7–3.8) *	7.1 (3.7–13.7) *
25 Gy	1.4 (0.8–2.4)	2.1 (1.3–3.2) *		2.9 (1.8–4.7) *	11.0 (5.4–22.0) *
					3.1 (1.3–7.6) *

[#] Models were adjusted for sex, race, cancer diagnosis, current age, years since cancer diagnosis, smoking, BMI, CHF, and treatment factors with p 0.2 on univariate analysis.

* p<0.05;

** The p-value for trend of lung radiation exposure is p=0.07 for asthma, p<0.001 for chronic cough, oxygen need, and lung fibrosis, and p=0.004 for recurrent pneumonia.

Table 4

Limitations in Daily Activity According to Pulmonary Outcomes

Pulmonary Condition	Activity Limitation – OR (95% CI) [#]		p-value for Survivors vs. Siblings
	Survivors	Siblings	
Asthma	1.7 (1.5–1.9) *	1.5 (1.2–1.8) *	0.32
Chronic Cough	2.7 (2.4–3.1) *	2.0 (1.5–2.6) *	0.04
Emphysema	2.2 (1.2–4.0) *	3.5 (1.1–11.7) *	0.49
Oxygen Need	3.0 (2.7–3.4) *	2.3 (1.6–3.1) *	0.09
Lung Fibrosis	2.3 (1.9–2.7) *	2.6 (1.3–5.4) *	0.74
Recurrent Pneumonia	3.2 (2.6–4.0) *	1.8 (1.0–3.4)	0.08

[#] Odds Ratio of survivors with a pulmonary condition reporting activity limitation compared to survivors without that pulmonary condition, and siblings with a pulmonary condition reporting activity limitation compared to siblings without that pulmonary condition. All models were adjusted for sex, race, age at questionnaire, smoking, BMI, amputation, paralysis, and congestive heart failure. CNS tumor survivors excluded.

* p<0.05