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Respiratory morbidity in young people surviving cancer: population-based study of hospital admissions, treatment-related risk factors and subsequent mortality

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Short title: Respiratory hospitalisation in long-term survivors of childhood and young adult cancers

Key words: children, adolescents and young adults, respiratory, hospitalisation, late effects

Abbreviations: AYA: adolescents and young adults CCS: childhood cancer survivors; CCSS: Childhood Cancer Survivors Study; CNS: Central nervous system; CI: confidence interval; CIF: cumulative incidence function; DAG: Directed acyclic graph; HES: Hospital Episode Statistics; HRR: Hospitalisation rate ratio; HR: hazard ratio; ICCC-3: International Classification of Childhood Cancers – version 3; ICD-10: International Classification of Diseases, version 10; NHS: National Health Service; SMR: Standardised Mortality Ratio; sHR: subdistribution hazard ratio; YSRCCYP: Yorkshire Specialist Register of Cancer in Children and Young People

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Novelty and impact

Respiratory diseases are a major cause of late morbidity and mortality amongst childhood cancer survivors. This population-based study provides comprehensive analysis of hospitalisations for respiratory conditions, the associated risks of admission by earlier cancer treatment and trends in readmissions and subsequent mortality in long-term survivors of cancers diagnosed under 30 years. The risk of hospitalisation was significantly higher in cancer survivors compared to the general population. Pulmonary toxic chemotherapy was associated with an increased risk of admissions for all respiratory disease especially pneumonia. Subsequent mortality was highest in those admitted for pneumonia compared to other respiratory conditions.

Abstract
Respiratory diseases are a major cause of late morbidity and mortality amongst childhood cancer survivors. This population-based study investigates respiratory hospital admissions in long-term survivors of cancers diagnosed in young people to identify specific respiratory morbidities, treatment-related risks and their relationship to subsequent morbidity and mortality. Population-based cancer registrations in Yorkshire, England, diagnosed between 1990 and 2011 aged 0-29 years, were linked to inpatient Hospital Episode Statistics (HES) for admissions up to 2017. All 5-year survivors were included in analysis (n=4235). Admission rates were compared to age- and sex- matched general population rates. Competing risk regression models were used to assess associations between treatment exposures and risk of admission. Risk of death following admission was calculated using Cox regression. By age 40, cumulative incidence for an admission for any type of respiratory condition was 49%. Respiratory admission rates were 1.86 times higher in cancer survivors than in the general population (95% Confidence Interval (CI) 1.73-2.01), and varied by respiratory condition and age at diagnosis. Treatment with chemotherapy with known lung toxicity increased the risk of admission for all respiratory conditions (subdistribution Hazard ratio (sHR)=1.26, 95%CI 1.03-1.53) and pneumonia (sHR= 1.48, 95%CI 1.01-2.17). Subsequent mortality was highest in those admitted for pneumonia compared to other respiratory conditions (28% and 15% respectively). Survivors of childhood and young adult cancer remain at significantly increased risk of respiratory complications several decades after treatment, emphasising the importance for clinical initiatives for prevention, early detection and treatment.

Introduction

Survival from childhood cancer has improved substantially over recent decades, with over 80% of children diagnosed with cancer in 2015 in England estimated to survive 10 years.[1] However, survivors are at increased risk of the late effects of their treatment, with over two-thirds of five-year survivors living with at least one chronic health condition.[2] Respiratory conditions are a leading cause of late mortality and morbidity in long-term childhood cancer survivors (CCS). Standardised mortality ratios for respiratory disease are between 3 and 9 times higher for CCS compared to the general population.[3-9] However, a decrease in the risk of death from respiratory diseases has been observed for children diagnosed more recently as cancer treatments have been modified to reduce long-term side effects.[9, 10] A recent UK study investigating respiratory mortality in survivors of cancer diagnosed before age 40 years found that pneumonia was the most common cause of respiratory death.[9]

Respiratory morbidity ranges in severity from subclinical to severe and life threatening complications which may impact on quality of life.[11-13] Available intelligence to date on respiratory morbidity is predominantly obtained by self-report and/or utilises sibling control data. Studies have shown that CCS have an increased risk of various respiratory conditions including lung fibrosis, pneumonia, chronic cough, pleurisy, use of supplemental oxygen, abnormal chest wall and exercise-induced shortness of breath, compared to sibling controls.[13-16] Limitations of using sibling controls are that both the CCS and the sibling control are likely to share the same environmental and genetic risk factors, therefore the true excess risk of respiratory disease in CCS may be under-estimated. Furthermore studies reliant upon patient-self report and completion of questionnaires may be prone to recall and selection bias, the latter point restricting the ability to generalise to the population.

Studies based upon hospital admissions have shown that the risk of hospitalisation for respiratory conditions are increased for CCS compared to the general population.[17-23] However, only one of these studies has looked at specific types of admissions for respiratory diseases.[18]

Individual and combined exposure to chest radiation, specific chemotherapy agents, haematopoietic stem cell transplants and thoracic surgery increase the risk of respiratory late effects among childhood cancer survivors.[11, 24, 25] The relationship between treatment exposure and hospital admissions for specific respiratory conditions in survivors of childhood and young adult cancers has not been described.

This study aims to 1) quantify the incidence of hospitalisations due to respiratory diseases in long-term survivors of childhood and young adult cancer, 2) identify treatment related risk factors associated with risk of respiratory admissions and 3) describe patterns of readmission and subsequent mortality in those hospitalised for respiratory conditions.

Methods

A long-term cancer survivor cohort was established from the Yorkshire Specialist Register of Cancer in Children and Young People (YSRCCYP) including all children and young people, aged 0-29 years, diagnosed between 1990 and 2011 and surviving at least 5-years from diagnosis. The YSRCCYP is a population-based database of children and young people diagnosed with cancer residing in the Yorkshire and Humber region in the north of England, covering a population of approximately 2 million 0-29 year olds. The primary source of ascertainment was hospital records with secondary sources including pathology reports, hospital admissions and other regional and national cancer registries.[26] All patients are proactively followed-up every two years to ascertain their vital status with minimal loss to follow-up.

Respiratory outcomes

The cancer survivor cohort was linked to inpatient Hospital Episode Statistics (HES) available between April 1997 and March 2017. Linkage was based on NHS number, date of birth, gender and postcode and conducted by NHS Digital using their standard deterministic algorithm.[27]

Data on respiratory admissions were identified from inpatient HES occurring at least five-years post diagnosis. Diagnoses for respiratory conditions were identified from the primary diagnosis field and all secondary diagnosis fields within each admission record in HES to ensure all admissions for respiratory conditions were identified. Respiratory admissions were classified based on ICD-10 codes: 1) any respiratory condition (J00-J99), 2) asthma (J45-J46), 3) pneumonia (J10.0, J11.0, J12-J18), 4) chronic lower respiratory disease (J40-J44, J47), 5) lung fibrosis (J84.1), and 6) respiratory conditions due to other external agents (J70) (this includes radiation and drug-induced lung disorders). To quantify hospitalisations due to respiratory conditions the first admission for each disease type was included. Readmissions following first admissions were identified.

Patient and treatment related variables

Patient, diagnosis and treatment related variables were extracted from the YSRCCYP including: age at diagnosis (children 0-14 years and adolescents and young adults (AYA) 15-29 years at diagnosis), sex, cancer diagnosis based on the International Classification of Childhood Cancers third edition (ICCC-3) [28] for children and the Birch classification [29] for AYA, date of diagnosis, Townsend area level deprivation based on postcode at diagnosis,[30] along with chemotherapy, radiotherapy and surgery details. Patients who had received any chemotherapy drugs with known pulmonary toxicity (bleomycin, busulphan, carmustine, cyclophosphamide and lomustine) were identified. Site of radiotherapy was extracted and radiotherapy to the chest included radiotherapy to the lungs, heart and mediastinum as well as total body irradiation. Thoracic surgery included operations of the chest wall, lobectomy and other operations on the lung.

Date of first admission for each respiratory condition was extracted and the time to first admission for each condition was calculated starting from 5 years after the diagnosis date. All cancer survivors were followed-up to the date of first admission for each respiratory disease, date of death or the censor date of 31/03/2017, whichever occurred first. Subsequent mortality following an admission for respiratory conditions was calculated from the date of the first admission.

Admissions in the general population

In order to establish if the admission rates for respiratory disease were higher in the cancer survivor cohort compared to the general population, individual level inpatient admission data for the whole Yorkshire and Humber region were obtained matching the cancer survivor cohort in terms of age and sex over the same time period. These data were used to estimate admission rates in the general population for each specified respiratory condition using population denominator data based on single-year of age, sex and calendar year for the Yorkshire and Humber region obtained from the Office for National Statistics.[31]

Statistical methods

Admission rates in the general population were used to calculate the expected number of admissions in the cancer survivor cohort and indirect standardisation techniques were used to obtain the hospitalisation rate ratio (HRR) standardised to the general population by age, sex and year.[32] HRRs were calculated for all ages and separately for children and AYA.

The cumulative incidence for each respiratory condition based on attained age was calculated, treating death as a competing risk.[33]

To assess the association between treatment exposures and respiratory admissions within the cancer survivor cohort competing risk regression models,[34] were used where death without hospitalisation for a respiratory condition was considered a competing risk. These models estimate the association between a set of covariates and the cumulative incidence function (CIF) described by the subdistribution hazard ratio (sHR). The sHR cannot be used to directly quantify the magnitude of the association but can be used to describe the direction of the observed association (similar to the hazard ratio).[35, 36]

Models were included for: 1) any respiratory admission, 2) asthma, 3) pneumonia and 4) chronic lower respiratory disease. Models were not included for lung fibrosis and conditions due to other external agents because of a small number of observed admissions (fewer than 10 admissions). For each treatment exposure (pulmonary toxic chemotherapy, chest radiation, and thoracic surgery), unadjusted and adjusted models were fitted. We used directed acyclic graphs (DAGs) implemented in DAGitty [37] to select a minimal sufficient adjustment set of variables to allow estimation of an unconfounded effect of each treatment exposure on respiratory admissions[38] From the DAG (available at dagitty.net/m6dZKD2) the minimal sufficient adjustment set included deprivation, diagnosis age, diagnosis year, diagnostic group and treatment exposures. Further models were examined including an interaction term between age group (children and AYA) and pulmonary toxic chemotherapy and chest radiation to determine whether the association between treatment and risk of admission differed by age. No interaction models were included for thoracic surgery due to small numbers.

Subsequent admission and mortality were examined for those admitted for at least one respiratory condition. Cox regression models were used to estimate the risk of subsequent mortality comparing those whose first admission (five-years post diagnosis) was for pneumonia compared to those admitted for other respiratory conditions.

Sensitivity analyses was conducted to estimate the HRR and cumulative incidence for each cause of respiratory admission based on the primary diagnosis field within each hospital admission only.

Results

A total of 4235 five-year cancer survivors were included; 32% had received chemotherapy drugs that are known to be pulmonary toxic, 4% had received radiation to the chest, while 0.7% had thoracic surgery (table 1). A total of 667 cancer survivors (15.7%) were admitted to

hospital for at least one respiratory condition (table 1). Supplementary table 1 shows the number of admissions for each ICD-10 respiratory chapter heading. There were different admission patterns by diagnostic group (supplementary figure 1).

The cumulative incidence for admissions for any respiratory disease, asthma and pneumonia increased with attained age without reaching a plateau (Figure 1). By age 40, the cumulative incidence for an admission for any type of respiratory condition was 49.3% (95%CI 44.6 to 53.7), asthma was 20.2% (95%CI 17.6 to 23.0), pneumonia was 13.2% (95%CI 8.2 to 19.5) and lower respiratory disease was 3.3 (95%CI 2.1 to 4.6).

For all respiratory conditions the risk of hospitalisation was 1.86 (95%CI 1.73 to 2.01) times higher in cancer survivors compared to the general population (table 2). For each respiratory condition the excess risk was significantly higher and was highest for respiratory conditions due to external agents (HRR=162, 95%CI 73 to 360) and lung fibrosis (HRR=13, 95%CI 6.5 to 26). However, these two outcomes were based on fewer than 10 observed cases and wide variations in the estimated confidence intervals. The HRR was 3.9 (95%CI 3.27 to 4.59) for pneumonia, 3.6 (95%CI 2.70 to 4.78) for lower respiratory conditions and 1.5 (95%CI 1.34 to 1.69) for asthma. The excess risk of hospitalisation was greater for childhood cancer survivors compared to survivors of AYA cancers, particularly for pneumonia and lower respiratory conditions. Stratifying by diagnostic group (Supplementary table 2) the excess risk for all respiratory conditions was similar for leukaemia, lymphoma, CNS tumours and carcinomas (AYA only), however there was no excess risk of admissions for those diagnosed with germ cell tumours.

After adjustment for confounders, an increased risk of admission was found in those treated with pulmonary toxic chemotherapy for any respiratory disease (sHR=1.26, 95%CI 1.03 to 1.53) and pneumonia (sHR=1.48, 95%CI 1.01 to 2.17) (Table 3, supplementary table 2). Thoracic surgery was associated with an increased risk of admission for lower respiratory disease (sHR=8.7, 95%CI 2.6 to 28.9). Significant interactions between age and chest radiotherapy were observed for all respiratory admissions, asthma and lower respiratory disease with an increased risk of admission observed in children but not in AYA (Table 4).

Following an admission for any respiratory condition, 45% were readmitted at least once for another respiratory condition. For those admitted for pneumonia (n=134), 25% were readmitted at least once for the same condition (supplementary table 4). Overall, 109 deaths were observed in those admitted for any respiratory conditions (table 5). The risk of death

doubled for those whose first admission was for pneumonia compared to those whose first admission was for another respiratory disease (95%CI 1.24 to 3.23).

Based on the primary admission diagnosis only, 352 survivors were admitted for a respiratory disease which was 1.8 times higher compared to the general population (95%CI 1.64 to 2.02) (supplementary table 5). The admission rate for asthma was similar in the cancer survivors and the general population. The cumulative incidence by age 40 for an admission for any type of respiratory condition was 32.9% (95%CI 27.5 to 38.3) (supplementary figure 2).

Discussion

Long-term survivors for childhood and young adult cancers were hospitalised for respiratory conditions twice as often as population comparisons; this excess risk varied by respiratory disease type and was greater for those diagnosed in childhood aged 0-14 compared to 15-29 year olds. The cumulative incidence of admissions continued to increase throughout life, reaching 50% by age 40. Pulmonary toxic chemotherapy was associated with an increased risk of admission and in particular admissions for pneumonia, while radiation to the chest increased the risk of admission in children but not for AYA. Long-term survivors admitted for pneumonia had an increased risk of subsequent death following admission compared to those admitted for other types of respiratory disease.

Linked hospital admissions were used as an objective measure of disease burden, compared to other studies of long-term survivors which rely upon self-reported outcomes. However, there are issues and complexities associated with this approach. Within each hospital admission the primary reason for admission is recorded along with (up to 20) secondary diagnostic codes mainly representing co-morbidities. The cumulative incidence of respiratory admission by age 40 based on all diagnostic codes was 50% compared to 33% when based on the primary admission only, the largest difference being in asthma admissions (20% falling to 2%), with no excess risk in hospitalisation compared to the general population. This implies that while asthma is a common co-morbidity in long-term cancer survivors it is not the main reason for subsequent hospitalisation. This is consistent with asthma more generally in the UK where the majority of asthma patients have mild disease mainly treated within primary care without experiencing exacerbation requiring hospitalisation.[39]

Based on the primary admission rates our cumulative incidence results are similar to other published studies (33% by age 40). The North American Childhood Cancer Survivors Study

found the cumulative incidence of any pulmonary condition by age 45 was 30%, [13] in Switzerland the cumulative incidence of respiratory disease 35 years after cancer diagnosis was 21%, [16] and the St Jude Lifetime Cohort Study found cumulative incidence by age 40 of 42% [40], which is higher but still lower than our cumulative incidence based on all diagnoses. Direct comparison between studies is difficult and the differences in cumulative incidence may be due to different methods of event ascertainment (hospital admissions vs self-report vs clinical assessment), different time periods of recruitment or different age ranges included, we included those diagnosed up to 29 years whereas in other studies the upper age limit was 21 years. However, one notable difference was the cumulative incidence of lung fibrosis We found the cumulative incidence of lung fibrosis was <1 % by age 40, however, it was reported to be 5% in the CCSS at age 45 years and 3% 35-years post diagnosis in Switzerland. The lower rate observed in our study may be due to differences in treatments relating to better outcomes or due to coding issues associated with using routine health data. Furthermore, it is unclear from our study if the respiratory admissions are isolated late effects or due to complications of recurrent cancer. Relapse rates prior to first admission for respiratory conditions were slightly higher for those first admitted with pneumonia (29%) compared to those admitted for other respiratory conditions (19%).

Admissions for pneumonia and lower respiratory diseases were 3.5-4 times more likely in cancer survivors compared to the general population. In a large Scandinavian record linkage study, admissions for pneumonia were 2.8 times higher and admission for bronchitis and emphysema were double in CCS compared to population controls.[18] We found a significant increased risk of pneumonia admissions for those treated with pulmonary toxic chemotherapy and an increased risk of subsequent mortality for those admitted with pneumonia compared to admissions for other respiratory conditions. Pneumonia is the most common cause of respiratory deaths [9] and CCS with recurrent pneumonia are more likely to have limitations with daily living activities, [13] therefore identifying those at greatest risk is important in order to identify preventative strategies, such as influenza and pneumococcal vaccinations.

A key strength of this study is the inclusion of those diagnosed up to age 29 years, compared to previous studies of respiratory morbidity which only include those diagnosed up to age 21. [13-16] We found higher excess risks of admission for those diagnosed in childhood compared to those diagnosed with cancer between 15-29 years for pneumonia and lower respiratory conditions. This supports recent findings showing that children have a greater respiratory mortality (SMR of 6.8) than those aged 15 to 39 years at diagnosis (SMR 1.7) with differences in mortality from pneumonia evident (SMR 8.2 in children and 2.1 in AYA).[9]

The association between receiving pulmonary toxic chemo and the risk of admission was similar in both age groups, however, we found a significant association between radiation to the chest and hospital admissions for those diagnosed as children but not at older ages. This would appear to support previous studies that have identified those diagnosed at younger ages to be more likely to have abnormal respiratory function.[11, 15, 25, 41]

Other key strengths of this research are the use of population-based data with general population controls, an objective outcome measure and the inclusion of detailed treatment information. Our analysis included young people diagnosed within one region in England, however, the Yorkshire is similar to the rest of the UK in term of socio-demographics therefore these results may be generalisable to the rest of England.[42] The main limitation of this study is that hospital admission data measures only the severe end of the disease spectrum whilst many respiratory conditions will be managed and treated within a primary care setting. Hence our findings may be a potential underestimation of the true extent of respiratory disease burden. HES data were available from 1997 onwards, in our study patients who were diagnosed in 1990-1991 did not start follow-up 5-years from diagnosis but shortly after when admission data were available. The linkage rate to HES was also slightly lower for these individuals therefore for those diagnosed in the earlier time period there may be an underestimation of admissions. The accuracy and completeness of recording of admissions for respiratory disease from HES, will have increased over the study period, particularly with the introduction of Payments By Results in 2002/03.[43] Restricting our analysis to those diagnosed after this period we found the HRR for all admission was slightly higher (2.7 (95%CI 2.4, 3.1) compared to over the whole time period and also found a steady increase in HRRs over the three periods of analysis for asthma. It is likely that this may have influenced our results to some degree. Further research evaluating the consistency between HES, primary care and self-reported data on respiratory illness is needed. Lifestyle risk factor data, such as smoking, height, weight and body mass index, were not available.

Conclusion

Respiratory morbidity is a serious long-term consequence following treatment for childhood and young adult cancers which may affect quality of life. Hospitalisations for respiratory conditions increase with age and admission rates are higher among long-term survivors compared to the general population. We identified an increased risk of subsequent morbidity and mortality following admissions for pneumonia, highlighting the need for life-long clinical monitoring of respiratory health to aid prevention and early identification and treatment for respiratory complications.

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Ethics approval

The YSRCCYP has ethical approval from the Northern and Yorkshire Research Ethics Committee (MREC/00/03/001) and approval for holding identifiable patient data from the Health Research Authority Confidentiality Advisory Group under section 251 of the NHS Act (2006).

Author Contributions

LS, AWG, RGF designed the study. LS analysed the data and drafted the manuscript. LS, AWG, DCG, DP and RGF contributed to the in interpretation of the results and critical revision of the manuscript. All authors approved the final manuscript.

Competing interests

None declared

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Tables

Table 1: Patient characteristics overall and by respiratory admission

	All (N=4235)		Respiratory admission (N=667)		No respiratory admission (N=3568)	
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**
Age group (at diagnosis)						
0-4 years	756	17.8	144	21.6	612	17.2
5-9 years	426	10.1	73	10.9	353	9.9
10-14 years	426	10.1	77	11.5	349	9.8
15-19 years	623	14.7	97	14.5	526	14.7
20-24 years	838	19.8	110	16.5	728	20.4
25-29 years	1166	27.5	166	24.9	1000	28.0
Sex						
Males	2555	60.3	332	49.8	2223	62.3
Females	1680	39.7	335	50.2	1345	37.7
Period of diagnosis						
1990-1996	1185	28.0	253	37.9	932	26.1
1997-2003	1309	30.9	241	36.1	1068	29.9
2004-2011	1741	41.1	173	25.9	1568	44.0
Deprivation quintile						
1 (least deprived)	252	6.0	30	4.5	222	6.2
2	515	12.2	79	11.8	436	12.2
3	857	20.2	130	19.5	727	20.4
4	893	21.1	151	22.6	742	20.8
5 (most deprived)	1718	40.6	277	41.5	1441	40.4
Pulmonary toxic chemotherapy						
No	2893	68.3	454	68.1	2439	68.4
Yes	1342	31.7	213	31.9	1129	31.6
Radiotherapy to chest						
No	4066	96.0	627	94.0	3439	96.4
Yes	139	4.0	40	6.0	129	3.6
Thoracic surgery						
No	4207	99.3	661	99.1	3546	99.4
Yes	28	0.7	6	0.9	22	0.6
Diagnostic group for children (0-14 years)	**(N=1608)**		**(N=294)**		**(N=1314)**	
ICCC diagnostic group	**n**	**%**	**n**	**%**	**n**	**%**
Leukaemia	522	32.5	11	37.8	411	31.3
Lymphoma	202	12.6	36	12.2	166	12.6
CNS tumours	344	21.4	68	23.1	276	21.0
Neuroblastoma	82	5.1	7	2.4	75	5.7
Retinoblastoma	65	4.0	7	2.4	58	4.4
Renal tumours	103	6.4	24	8.2	79	6.0
Bone tumours	54	3.4	6	2.0	48	3.7
Soft tissue sarcoma	104	6.5	15	5.1	89	6.8
Germ cell tumours	79	4.9	10	3.4	69	5.3
Other†	53	3.3	10	3.4	43	3.3
Diagnostic group for AYA (15-29 years)	**(N=2627)**		**(N=373)**		**(N=2254)**	
Birch Classification group	**n**	**%**	**n**	**%**	**n**	**%**
Leukaemia	201	7.7	31	8.3	170	7.5

Lymphoma	745	28.4	122	32.7	623	27.6
CNS tumours	273	10.4	35	9.4	238	10.6
Bone tumours	98	3.7	23	6.2	75	3.3
Soft tissue sarcoma	113	4.3	19	5.1	94	4.2
Germ cell tumours	779	29.7	75	20.1	704	31.2
Carcinomas	383	14.6	63	16.9	320	14.2
Other††	35	1.3	5	1.3	30	1.3

†Other diagnostic group for children includes hepatic, other epithelial and other unspecified

††Other diagnostic group for AYA includes melanoma and skin cancer, miscellaneous and unspecified neoplasms

Abbreviations: ICCC: International Classification of Childhood Cancers (version 3); CNS: central nervous system; AYA: adolescents and young adults

Table 2: Observed and expected admissions and hospitalisation rate ratio (HRR) comparing admissions among cancer survivors with the general population by age at diagnosis

	Observed admissions n (%)	Expected admissions	HRR (95% CI)
All ages (N=4235)			
Any respiratory admission	667 (15.7)	358	1.86 (1.73, 2.01)
Asthma	289 (6.8)	192	1.51 (1.34, 1.69)
Pneumonia	134 (3.2)	35	3.87 (3.27, 4.59)
Chronic lower respiratory disease	47 (1.1)	13	3.59 (2.70, 4.78)
Lung fibrosis	8 (0.2)	1	13.1 (6.5, 26.1)
Respiratory conditions due to other external agents	6 (0.1)	0.04	162 (73, 360)
Children (0-14 years at diagnosis) (N=1608)			
Any respiratory admission	294 (18.3)	143	2.05 (1.83, 2.30)
Asthma	115 (7.2)	75	1.54 (1.28, 1.85)
Pneumonia	63 (3.9)	10	6.52 (5.09, 8.35)
Chronic lower respiratory disease	17 (1.1)	2	9.4 (5.85, 15.14)
AYA (15-29 years at diagnosis) (N=2627)			
Any respiratory admission	373 (14.2)	214	1.74 (1.57, 1.93)
Asthma	174 (6.6)	117	1.49 (1.29, 1.73)
Pneumonia	71 (2.7)	25	2.85 (2.26, 3.60)
Chronic lower respiratory disease	30 (1.1)	11	2.66 (1.86, 3.80)

For children and AYA HRR not calculated for lung fibrosis or respiratory conditions due to other external agents due to small numbers

Abbreviations: HRR: hospitalisation rate ratio; CI; confidence interval; AYA: adolescents and young adults

Table 3: Association between treatment exposure and risk of admission for respiratory disease with death as a competing risk, adjusted model results

		Any respiratory admission		Asthma		Pneumonia		Chronic lower respiratory disease	
		n*	**sHR (95%CI) †**	**n***	**sHR (95%CI) †**	**n***	**sHR (95%CI) †**	**n***	**sHR (95%CI) †**
Treatment exposure									
Pulmonary toxic chemotherapy	No	454	1.0	204	1.0	80	1.0	30	1.0
	Yes	213	1.26 (1.03, 1.53)	85	0.86 (0.65, 1.13)	54	1.48 (1.01, 2.17)	17	0.98 (0.50, 1.94)
Chest radiotherapy	No	627	1.0	272	1.0	123	1.0	42	1.0
	Yes	40	1.24 (0.87, 1.78)	17	1.23 (0.72, 2.12)	11	1.25 (0.64, 2.43)	5	1.34 (0.43, 4.16)
Thoracic surgery	No	661	1.0	287	1.0	132	1.0	44	1.0
	Yes	6	1.38 (0.59, 3.25)	**	0.96 (0.23, 4.03)	**	2.25 (0.56, 8.98)	**	8.67 (2.60, 28.9)

n* number of admissions for each condition
** Numbers in groups with 5 or fewer people have been suppressed due to potential identifiability of cases
† model adjusted for deprivation, diagnosis age, diagnosis year, diagnostic group, and treatment exposures
Abbreviations: sHR: subdistribution hazard ratio; CI: confidence interval

Table 4: Association between treatment exposure and risk of admission for respiratory disease with death as a competing risk including interaction with age group, adjusted models

Outcome	Treatment exposure	Children		AYA		Interaction p
		n*	sHR (95%CI) †	n*	sHR (95%CI) †	
Any respiratory admission	Pulmonary toxic chemotherapy					
	No	215	1.0	239	1.0	0.42
	Yes	79	1.36 (1.03, 1.80)	134	1.18 (0.92, 1.51)	
	Chest radiotherapy					
	No	284	1.0	343	1.0	0.003
	Yes	10	3.32 (1.68, 6.57)	30	1.01 (0.68, 1.51)	
Asthma	Pulmonary toxic chemotherapy					
	No	86	1.0	118	1.0	0.50
	Yes	29	1.10 (0.70, 1.73)	56	0.91 (0.63, 1.31)	
	Chest radiotherapy					
	No	111	1.0	161	1.0	0.05
	Yes	**	3.21 (1.14, 9.01)	**	0.99 (0.54, 1.80)	
Pneumonia	Pulmonary toxic chemotherapy					
	No	42	1.0	38	1.0	0.76
	Yes	21	1.90 (1.09, 3.32)	33	1.69 (0.97, 2.96)	
	Chest radiotherapy					
	No	62	1.0	61	1.0	
	Yes	**	0.88 (0.12, 6.65)	**	1.27 (0.61, 2.60)	0.74
Chronic lower respiratory disease	Pulmonary toxic chemotherapy					
	No	10	1.0	20	1.0	
	Yes	7	2.03 (0.73, 5.68)	10	0.59 (0.26, 1.32)	0.06
	Chest radiotherapy					
	No	14	1.0	28	1.0	
	Yes	**	15.52 (3.58, 67.2)	**	0.50 (0.11, 2.31)	0.001

n* number of admission for each condition

** Numbers in groups with 5 or fewer people have been suppressed due to potential identifiability of cases, other cells have also been supressed to avoid disclosure by differencing

Interaction models between thoracic surgery and age group could not be fitted due to small numbers.

† sHRs from adjusted interaction model, adjusting for deprivation, year of diagnosis, diagnosis group and other treatment risk factors

Abbreviations: AYA: adolescents and young adults; sHR: subdistribution hazard ratio; CI: confidence interval

Table 5: Mortality following first admissions for respiratory disease for long-term survivors

First admission	N	Subsequent deaths (%)	1 year survival (%) † (95% CI)	Adjusted HR ††
All	667	109 (16%)	92 (89, 94)	-
Pneumonia	86	24 (28%)	84 (74, 90)	2.00 (1.24, 3.23)
Other respiratory conditions	581	85 (15%)	93 (91, 95)	1.0 -

† Survival measured from date of first admission five-years post diagnosis

†† model adjusted for deprivation, diagnosis age, diagnosis year, diagnostic group, and treatment exposures

Abbreviations: HR: Hazard ratio

Figure legend
Figure 1: Cumulative incidence of respiratory admission by attained age