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Cumulative burden of subsequent neoplasms, cardiovascular and respiratory morbidity in young people surviving cancer

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Highlights

- Survivors of childhood cancer have increased risk of multiple and recurrent disease
- Cumulative risk of hospitalisations for cardiovascular or respiratory conditions, or cancer registration for SMN analysed
- Cardiovascular and respiratory morbidity measured by hospital admissions
- 10-years post-diagnosis an average of 13 events per 100 survivors were observed

Abbreviations

AYA: Adolescents and young adults; CI: confidence interval; CNS: Central Nervous System; DAG: Directed acyclic graph; HES: Hospital Episode Statistics; HR: hazard ratio; ICD-10: International Classification of Diseases version 10; IQR: Interquartile range; NCRAS: National Cancer Registration and Analysis Service; PWP-TT: Prentice, Williams and Peterson total time; sHR: sub-distribution hazard ratio; SMN: Subsequent Malignant Neoplasm; YSRCCYP: Yorkshire Specialist Register of Cancer in Children and Young People.

Abstract

Background

Long-term childhood and young adult cancer survivors are at increased risk of the late effects of multiple chronic conditions. In this study we estimate the cumulative burden of subsequent malignant neoplasms (SMN), cardiovascular and respiratory hospitalisations in long-term survivors of childhood and young adult cancers and associated treatment risks.

Methods

Five-year survivors of cancer diagnosed aged 0-29 years between 1992-2009 in Yorkshire, UK were included. The cumulative count of all hospital admissions (including readmissions) for cardiovascular and respiratory conditions and all SMNs diagnosed up to 2015 was calculated, with death as a competing risk. Associations between treatment exposures and cumulative burden were investigated using multiple-failure time survival models.

Results

A total of 3464 5-year survivors were included with a median follow-up of 8.2 years (IQR 4-13 years). Ten-years post diagnosis, the cumulative incidence for a respiratory admission was 6.0% (95%CI 5.2 to 6.9), a cardiovascular admission was 2.0% (95%CI 1.5 to 2.5), and SMN was 1.0% (95% CI 0.7 to 1.4) with an average of 13 events per 100 survivors observed (95%CI 11 to 15). The risk of experiencing multiple events was higher for those treated with chemotherapy drugs with known lung toxicity (HR=1.35, 95%CI 1.09-1.68).

Discussion

Survivors of childhood and young adult cancer experience a high burden of morbidity due to respiratory, cardiovascular diseases and SMNs up to 20-years post-diagnosis. Statistical methods that capture multiple morbidities and recurrent events are important when quantifying the burden of late effects in young cancer survivors.

1. Introduction

It is currently estimated in the UK that over 80% of children, adolescents and young people diagnosed with cancer will survive for at least 5-years adding to a growing population of long-term survivors [1, 2]. However, these long-term survivors are at an increased risk of the late effects of their treatment with over two-thirds living with at least one chronic health condition and over one third reporting at least 2 conditions [3].

The leading causes of late mortality and morbidity are subsequent malignant neoplasms (SMN), cardiovascular and respiratory disease [3-6]. Many studies of the late effects in childhood cancer survivors focus on single disease areas, however long-term survivors are at increased risk of multiple morbidities and recurrent disease. Common epidemiological measures such as the incidence or prevalence of single conditions do not adequately capture the wider burden of late effects in long-term cancer survivors. Epidemiological studies are therefore needed which utilise methods applicable to capture complex disease trajectories [7].

Previous research based on long-term survivors of childhood and young adults cancers in Yorkshire in the UK, has shown that they are at increased risk of hospitalisations for both cardiovascular disease [8] and respiratory disease [9]. Both these studies estimated the cumulative incidence based on time to first hospital admission only. In this study we examine the combined incidence of SMNs, cardiovascular and respiratory hospitalisations (as a marker of morbidity), including all readmissions, in the same cohort of long-term survivors of childhood and young people's cancer, focussing on differences by previous treatment.

2. Materials and methods

2.1 Study population

Information on long-term cancer survivors was extracted 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 1992 and 2009 and surviving for at least 5-years from diagnosis. The YSRCCYP is a population-based database of all children and young people (0-29 years) diagnosed with cancer residing in the Yorkshire and Humber region in the north of England [10]. The primary source of ascertainment was hospital records with secondary sources including pathology reports, hospital admissions and other regional and national cancer registries. All patients were proactively followed-up every two years to ascertain their vital status with minimal loss to follow-up (<0.1%).

2.2 Outcomes

2.2.1 Respiratory and cardiovascular inpatient admissions

All cancer survivor records were submitted for linkage with inpatient Hospital Episode Statistics (HES) occurring between April 1997 and December 2015. Linkage was based on NHS number, date of birth, sex and postcode and conducted by NHS Digital using their standard deterministic algorithm [11]. Postcode was based on postcode at diagnosis and if different the persons current postcode. Linkage was to all admissions in England within this time period. HES inpatient admissions are recorded as a series of Finished Consultant Episodes which represent a period of care under a particular consultant specialty at a single hospital provider. For each individual, continuous inpatient spells were created to represent one admission, which included all continuous episodes of care which includes transfers between hospitals.

Admissions for any respiratory or cardiovascular condition were identified from inpatient HES occurring five-years post diagnosis for each individual. Inpatient HES are coded using ICD-10 and include a primary diagnosis field and up to 19 secondary diagnostic codes which include details of all

reported comorbidities. Diagnoses for any respiratory (ICD-10 J00-J99) or any cardiovascular (ICD-10 I00-I99, G45 and G46) condition were identified from the primary diagnosis field only for any episodes within an admission. Dates of all admissions were extracted.

2.2.2 Subsequent malignant neoplasms

Data on all SMNs were obtained from the YSRCCYP database and the National Cancer Registration and Analysis Service (NCRAS) [12]. SMNs were defined as a malignant neoplasm of any site with a different morphology from that of the primary tumour regardless of time since diagnosis according to the recommended coding of multiple primary cancers [13]. CNS tumours with benign or in-situ behaviour that are included in the International Classification of Childhood Cancer (ICCC-3) [14], such as pilocytic astrocytomas and meningiomas, were also included. Non-melanoma skin cancers were excluded as there is known variation in registration of these tumours in England and not all tumours are reported [15]. If a patient was diagnosed with a SMN while under the age of 30 and resident in Yorkshire, then this is recorded in the YSRCCYP database. However, if the patient was 30 or older when diagnosed or was no longer resident in Yorkshire this information was obtained from the NCRAS. All SMNs diagnosed five-years post diagnosis up to 31st December 2015 were included.

2.3 Treatment

Treatment data were extracted from the YSRCCYP focussing on three treatment groups of interest: anthracyclines, chemotherapy drugs with known lung toxicity (bleomycin, busulphan, carmustine, cyclphoshamide and lomustine), and radiation to the chest (including radiotherapy to the lungs, heart and mediastinum as well as total body irradiation). A binary indicator was created for each treatment group as accurate dose information was not available.

2.4 Other patient characteristics

Other patient and diagnosis related variables were extracted from the YSRCCYP including: age group at diagnosis (children 0-14 years, adolescents and young adults (AYA) 15-29 years), sex, type of cancer diagnosed, date of diagnosis, Townsend area level deprivation based on postcode at diagnosis [16] and ethnicity split into three groups (White, South Asian and Other) based on a previously documented methodology [17].

2.5 Statistical analysis

The cumulative incidence for each event type (respiratory admission, cardiovascular admission or SMN diagnosis) was examined treating death as a competing risk [18]. Follow-up time started 5-years post diagnosis and ended at the date of event or date of death or end of follow-up (31st December 2015), whichever came first. Each individual had at least one full year of follow-up.

In addition to focussing on each event type independently, the cumulative burden of all three events was examined. This included multiple hospital admissions for respiratory and cardiovascular conditions and multiple SMN diagnoses. Supplementary Figure A.1 shows hypothetical examples for 5 individuals with different patterns of events.

The mean cumulative count was used to estimate the total burden of all hospitalisations for respiratory and cardiovascular disease and all SMNs. The mean cumulative count estimates the mean number of multiple and recurrent events per individual in the population within a given time period in a competing risk framework while also accounting for person time at risk and censoring [19].

To estimate the association between previous cancer treatment and cumulative burden of all events, adjusting for potential confounders, the Prentice, Williams and Peterson total time (PWP-TT)

survival model for multiple-failure times was used [20]. This model is an extension of the Cox model which allows for recurrent events for each individual. The PWP-TT model is a stratified model for ordered multiple events, where all individuals are at risk for the first stratum but only those with an event in the previous stratum are at risk for the successive one. Robust standard errors were estimated to account for correlations within individuals. The total time model was used which measured time to each event from the start of follow-up [21]. These models were not developed within a competing risk framework, therefore deaths were also considered as a failure event; this approach has been recommended for analysis of multiple hospital admissions [22]. Further models were considered stratifying by age at diagnosis and by diagnostic group.

Selection of potential confounders for adjustment in the regression models was based on causal inference methods and a directed acyclic graph (DAG) (Supplementary Figure A.2) implemented in DAGitty [23] to identify the minimal sufficient adjustment set of variables allowing estimation of an unconfounded effect of each treatment exposure on cumulative burden. The minimal sufficient adjustment set included diagnostic group, age at cancer diagnosis, year of diagnosis, deprivation, ethnicity and the other treatment exposures.

Sensitivity analysis was undertaken investigating the association between each treatment exposure and each outcome individually using competing risk regression modelling, which estimates the subdistribution hazard ratio (sHR) to show the associations between each treatment exposure and the cumulative incidence function [24].

3. Results

A total of 3464 five-year cancer survivors were included (1328 children and 2136 AYA) with a median follow-up starting 5-years post diagnosis of 8.2 years (interquartile range (IQR) 3.7 to 13.3 years). The median attained age was 32 years (IQR 24 to 40 years) (Table 1). A total of 280 (8%) survivors were admitted to hospital at least once for a respiratory condition, with 80 (2%) having 2 or more

respiratory admissions; 138 (4%) were admitted at least once for a cardiovascular condition, 37 (1%) of whom were admitted more than once for cardiovascular disease. 74 (2%) individuals were diagnosed with at least one SMN (Table 2). Supplementary Table A.1 shows a breakdown of the number of HES episodes by diagnostic code for all respiratory and cardiovascular admissions.

Ten-years post diagnosis, the cumulative incidence for a respiratory admission was 6.0% (95%CI 5.2 to 6.9), a cardiovascular admission was 2.0% (95%CI 1.5 to 2.5), and SMN was 1.0% (95% CI 0.7 to 1.4 (Figure 1A). Based on the mean cumulative count, 10-years post diagnosis a mean of 13 events per 100 survivors were observed (95%CI 11 to 15) (Figure 1B).

In unadjusted models there was no statistically significant association between any of the treatment exposures and risk of events (taking into account all and recurrent events) (Table 3). After full adjustment for confounders, the risk of an event was higher for those treated with pulmonary toxic chemotherapy (HR=1.35, 95%CI 1.09, 1.68); there was no statistically significant associations with anthracycline exposure (HR=0.95, 95%CI 0.75, 1.20) or radiation to the chest (HR=1.11, 95%CI 0.95, 1.86).

For childhood cancer survivors, the mean number of events per 100 survivor was 16 (95%CI 13 to 20) 10-years after diagnosis, while for AYA survivors 11 events per 100 survivors were observed (95%CI 8 to 13) (Supplementary Figure A.3). After full adjustment for confounders, the risk of experiencing an event was significantly increased for children treated with pulmonary toxic chemotherapy (HR=1.43, 95%C% 1.09 to 1.87) and radiation to the chest (HR=2.86, 95%CI 1.76 to 4.65) but no increased risk was observed for AYA (HR=1.03, 95%CI 0.82 to 1.31 and HR=1.20, 95%CI 0.81 to 1.78, respectively) (Table 4). No increased risk associated with anthracyclines was observed in either age group.

Analysis stratified by diagnostic group showed an increased risk of an event for children with CNS tumours treated with pulmonary toxic chemotherapy and for children with leukaemia who had radiation to the chest (this included total body irradiation) (Table 5).

The association between treatment exposure and time to first event for each outcome are shown in Supplementary Table A.2. After full adjustment for confounders, those treated with pulmonary toxic chemotherapy had a non-statistically significant increased risk of respiratory admissions (sHR= 1.30, 95% CI 0.92 to 1.85), cardiovascular admission (sHR= 1.47, 95% CI 0.94 to 2.30) and SMN diagnosis (sHR=1.80, 95% CI 0.97 to 3.32).

4. Discussion

In this population-based study we describe the combined burden of hospitalisations for respiratory and cardiovascular diseases and SMNs diagnosed in long-term survivors of childhood and young adult cancers including a median follow-up of 13 years from diagnosis. Ten-years post-diagnosis an average of 13 events per 100 survivors were observed with respiratory admissions accounting for the largest proportion of these events. After complete adjustment for confounders, there was a significant increased cumulative burden for those treated with pulmonary toxic chemotherapy but not for anthracyclines or radiation to the chest.

We restricted our analysis to three groups of conditions representing the most common causes of late mortality among long-term childhood cancer survivors. From the cumulative incidence trends (Figure 1), it can be seen that respiratory admissions have the largest contribution to the mean cumulative count. Other studies have shown that childhood and young adult cancer survivors have an increased risk of hospitalisations for cardiovascular and respiratory conditions compared to the general population [25-30]. However, these studies have been based on time to first admission only and no estimates were given of the cumulative burden of all hospitalisations.

The analysis was based on all cancers combined which may mask any differences by treatment within diagnostic groups. However, only limited analysis by diagnostic group was conducted due to the small sample size for the other diagnostic groups. Using a similar methodology, the SJLIFE study included 10-year childhood cancer survivors with outcomes based on clinical assessment and medical record validation (as opposed to hospitalisations in our study), which reported a cumulative burden by age 40 years of 2.55 per survivor for cardiovascular conditions, 0.75 for respiratory conditions and 0.45 for SMNs giving a total cumulative burden for these three conditions combined of 3.75 per individual [31]. Our outcome measure was based upon hospital admissions as a proxy measure of disease burden including the primary admission diagnosis within the HES record. Inpatient hospital admission data are likely to reflect the more severe end of the disease spectrum, with many respiratory and cardiovascular conditions being managed and treated within a primary care setting. Therefore our findings may be a potential underestimation of the true extent of disease burden.

After adjustment for potential confounders, we found that those treated with pulmonary toxic chemotherapy drugs had an increased cumulative burden of events, but there was no association with anthracycline exposure or receiving radiation to the chest. These findings concur with previous analyses based on this cohort [8, 9]. The mechanisms for this are unclear and more comprehensive studies incorporating accurate treatment dose information are required.

We were unable to estimate the cumulative burden of the Yorkshire survivor cohort in relation to that in the general population as no reference data existed combining cancer incidence and cardiovascular and respiratory hospitalisations. However, these conditions were selected based on prior knowledge of the increased risks compared to the general population [3-6]. Examination of national age-specific hospital admission patterns for respiratory and cardiovascular diseases

(Supplementary Figure A.4) and cancer incidence (Supplementary Figure A.5) show the risks increase steeply in the general population from the mid-40s and early 50s onwards. With further follow-up of this cohort into older ages, we would expect morbidity rates to increase further highlighting the need for life-long follow-up care for this population of long-term survivors.

The main limitation of this work is that different data sources were used to capture the three main outcome measures. Subsequent tumours were measured using registry data which does not capture any hospital admissions related to SMN. While HES admissions were used to measures outcomes related to respiratory and cardiovascular morbidity. Furthermore, no measures of length of stay were included which represents an important area for further research. A further limitation of our study is that in the statistical modelling, death was considered as an event, and given equal weighting as hospitalisation and SMN diagnosis. Ideally this would be considered in a competing risk framework, for example, through the application of more complex statistical methods such as multi-state models which represents an area for further research.

4.1 Conclusion

Long-term survivors of childhood and young adult cancer diagnosed between 1992 and 2009 experienced a high disease burden due to respiratory and cardiovascular disease and SMNs. Long-term follow up care is needed that accounts for the complexity of health needs for this high risk population.

Authors' contributions

Study conception and design: LS. AWG, RGF

Acquisition of the data: LS, RF

Analysis of the data: LS

Interpretation of the data: LS, AWG, DCG, RGF

Writing the article: LS

Critical revision of the article: All authors approved the final manuscript and the decision to submit the manuscript

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).

Declaration of Competing Interest

None

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Data availability

The data supporting the conclusions of this article are included within the article. The datasets generated and analysed during the current study are not publicly available due to the potential for disclosure of individuals' personal data.

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Figure legends

Figure 1: Cumulative incidence and cumulative burden of subsequent malignant neoplasms (SMN), respiratory and cardiovascular morbidity. A. Cumulative incidence for each event type (respiratory admission, cardiovascular admission, SMN). B. Mean cumulative count for all respiratory and cardiovascular admissions and all SMNs.

Tables

Table 1: Characteristics of the study population

		N=3464	
Characteristic		**n**	**%**
Age group (at diagnosis)	0-4 years	615	17.8
	5-9 years	356	10.3
	10-14 years	357	10.3
	15-19 years	506	14.6
	20-24 years	674	19.5
	25-29 years	956	27.6
Sex	Males	2069	59.7
	Females	1395	40.3
Period of diagnosis	1992-1997	879	25.4
	1998-2003	1309	37.8
	2004-2009	1276	36.8
Deprivation fifth	1 (least deprived)	203	5.9
	2	426	12.3
	3	703	20.3
	4	739	21.3
	5 (most deprived)	1394	40.2
Ethnic group	White	3010	86.9
	South Asian	264	7.6
	Other	130	3.8
	Missing	60	1.7
Anthracycline		1103	31.8
Pulmonary toxic chemotherapy		1127	32.5
Radiotherapy to chest		137	4.0
Attained age	Medan (IQR)	32	(24 to 40)
ICCC Diagnostic group [14] for children (0-14 years)		**(N=1328)**	
	Leukaemia	435	32.8
	Lymphoma	170	12.8
	CNS tumours	291	21.9
	Neuroblastoma	64	4.8
	Retinoblastoma	50	3.8
	Renal tumours	86	6.5
	Bone tumours	43	3.2
	Soft tissue sarcoma	85	6.4
	Germ cell tumours	64	4.8
	Other†	40	3.0
Birch Classification group [32] AYA (15-29 years)		**(N=2136)**	
	Leukaemia	161	7.5
	Lymphoma	596	27.9
	CNS tumours	218	10.2
	Bone tumours	84	3.9
	Soft tissue sarcoma	93	4.4
	Germ cell tumours	647	30.3
	Carcinomas	309	14.5
	Other††	28	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

Table 2: Summary of outcomes for cumulative burden analysis

Outcome	All N=3464 n (%)	Children N=1328 n (%)	AYA N=2136 n (%)
At least 1 respiratory admission	280 (8.1)	139 (10.5)	141 (6.6)
1 admission	*200 (5.8)*	*101 (7.6)*	*99 (4.6)*
2 admissions	*41 (1.2)*	*17 (1.3)*	*24 (1.1)*
3 admissions	*11 (0.3)*	-	-
4 admissions	*13 (0.4)*	-	-
5+ admissions	*15 (0.4)*	*8 (0.6)*	*7 (0.3)*
At least 1 cardiovascular admission	138 (4.0)	53 (4.0)	85 (4.0)
1 admission	*101 (2.9)*	38 (2.9)	*63 (2.9)*
2 admissions	*13 (0.4)*	-	-
3 admissions	*9 (0.3)*	-	-
4 admissions	*6 (0.2)*	-	-
5+ admissions	*9 (0.3)*	-	-
At least 1 SMN	74 (2.1)	27 (2.0)	47 (2.2)
Combined outcomes			
Respiratory and cardiovascular admission	37 (1.1)	16 (1.2)	21 (1.0)
Respiratory and SMN	15 (0.4)	6 (0.5)	9 (0.4)
Cardiovascular and SMN	7 (0.2)	-	-
All 3 events	<5	-	-

Cells with 5 or fewer cases have been suppressed due to potential identifiability of cases, other cells may be suppressed to avoid disclosure by difference.

Table 3: Association between treatment exposures and risk of events (respiratory or cardiovascular admission or subsequent neoplasm), hazard ratios (95%CI) from the PWP-TT model incorporating all and recurrent events.

Treatment	Unadjusted HR (95%CI)	Adjusted HR † (95%CI)
Anthracycline		
No	1.0 (ref)	1.0 (ref)
Yes	1.07 (0.92, 1.24)	0.95 (0.75, 1.20)
Pulmonary toxic chemotherapy		
No	1.0 (ref)	1.0 (ref)
Yes	1.11 (0.95, 1.29)	1.35 (1.09, 1.68)
Chest Radiotherapy		
No	1.0 (ref)	1.0 (ref)
Yes	1.34 (0.98, 1.83)	1.11 (0.95, 1.86)

†Adjusted model includes diagnostic group, age at cancer diagnosis, year of diagnosis, deprivation, ethnicity and the other treatment exposures.

Table 4: Association between treatment exposures and risk of events (respiratory or cardiovascular admission or subsequent neoplasm), adjusted hazard ratios (95%CI) from the PWP-TT model incorporating all and recurrent events, stratified by age at diagnosis

	Adjusted HR † (95%CI)	
Treatment	**Children**	**AYA**
Anthracycline		
No	1.0 (ref)	1.0 (ref)
Yes	1.19 (0.88, 1.61)	1.05 (0.78, 1.41)
Pulmonary toxic chemotherapy		
No	1.0 (ref)	1.0 (ref)
Yes	1.43 (1.09, 1.87)	1.03 (0.82, 1.31)
Chest Radiotherapy		
No	1.0 (ref)	1.0 (ref)
Yes	2.86 (1.76, 4.65)	1.20 (0.81, 1.78)

†Adjusted model includes diagnostic group, year of diagnosis and deprivation, ethnicity and the other treatment exposures

Table 5: Association between treatment exposures and risk of events (respiratory or cardiovascular admission or subsequent neoplasm), adjusted hazard ratios (95%CI) from the PWP-TT model incorporating all and recurrent events, stratified by diagnostic group and age at diagnosis

	Adjusted HR † (95% CI)		
Treatment	**Leukaemia 0-14 years N=435**	**CNS tumours 0-14 year N=291**	**Germ cell tumours 15-29 years N=657**
Anthracycline			
No	1.0 (ref)		
Yes	1.06 (0.64, 1.75)		
Pulmonary toxic chemotherapy			
No	1.0 (ref)	1.0 (ref)	1.0 (ref)
Yes	0.75 (0.44, 1.29)	3.07 (1.94, 4.84)	0.95 (0.65, 1.39)
Chest Radiotherapy			
No	1.0 (ref)		
Yes	4.95 (2.36, 10.4)		

†Adjusted for diagnostic group, age at cancer diagnosis, year of diagnosis, deprivation, ethnicity and the other treatment exposures

Anthracyclines and chest radiotherapy not included as treatment exposures for CNS or germ cell tumours

Chest radiotherapy includes total body irradiation for leukaemia patients