Cardiovascular sequelae in long term survivors of young people's cancer – a linked cohort study

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Key words: Cancer, Cardiovascular, Childhood, Teenage, Survivors, Late Effects

ABSTRACT

BACKGROUND: Cancer registration data (1991–2006) were linked to hospital admission data (1996–2011) to determine the incidence and risk of cardiovascular late effects (LEs) amongst long term survivors of childhood (0-14) and young adult (15-29) cancer in Yorkshire.

RESULTS: Of 3,247 survivors of cancer, 3.6% had at least one cardiovascular LE. Overall, cardiovascular hospitalisations for the childhood cohort were 3-fold higher compared to the general population, but did not differ for young adults. For young adults increased rates were limited to 'pericardial disease', 'cardiomyopathy and heart failure', 'pulmonary heart disease', 'hypertension' and 'conduction disorders'.

CONCLUSION: Survivors of childhood and young adults remain at increased risk of cardiovascular LEs compared to the general population.

INTRODUCTION

In the UK, approximately 80% of children and young people diagnosed with a malignancy can expect to become a long term survivor (Cancer Research UK, 2012; Stiller, 2007). However, this growing cohort are at increased risk of developing chronic health conditions including malignant neoplasms, neurocognitive impairment and cardiotoxicity, with approximately two–thirds of survivors developing at least one such condition (Oeffinger *et al*, 2006). Late effects (LEs) associated with survival from childhood cancer are increasingly well described although data reporting cardiovascular diseases identified from hospital episodes are limited (Blanco *et al*, 2011; Mulhern *et al*, 2004; Mulrooney *et al*, 2009; Neglia *et al*, 2001; Travis *et al*, 2012; Tukenova *et al*, 2010; van der Pal *et al*, 2012), whilst issues facing survivors diagnosed in young adulthood are even less clearly defined (Woodward *et al*, 2011). Furthermore, information has predominantly relied on self–reported outcomes in retrospective cohort studies (Mulrooney *et al*, 2009; Oeffinger *et al*, 2006), rather than more objective measures which may be achieved by the linkage of electronic health records (Hawkins, 2010; Zhang *et al*, 2013).

We have linked routinely collected population–based cancer registry data with administrative hospital admissions data, to quantify the incidence and risk of cardiovascular LEs amongst survivors of childhood and young adult cancer.

PATIENTS AND METHODS

Case data

The Yorkshire Specialist Register of Cancer in Children and Young People (van Laar *et al*, 2010) was used to identify long term survivors (at least 5-years post diagnosis) of childhood and young adult cancer (0-14 and 15-29 years inclusive) diagnosed between 1991 and 2006, providing at least five years follow–up data.

Hospital Admissions Data

Cases data were linked to inpatient HES data (1996–2011) using NHS number, date of birth, gender and postcode, cases were also linked to outpatient HES. Inpatient HES data were obtained for the general population resident within Yorkshire between 1996 and 2011 and matched by age at hospital admission to the survivors' cohort in the following age–period groups: 5-34 years in 1996, 5-35 years in 1997, up to 5-49 years in 2011.

Statistical Methods

Cardiovascular LEs were grouped as follows: 'hypertension', 'cardiomyopathy; heart failure', 'coronary artery disease', 'pulmonary heart disease', 'pericardial disease', 'valvular heart disease', 'conduction disorders', 'cerebrovascular disease' and 'operations and procedures requiring hospitalisation' based on ICD–10 diagnosis codes and OPCS–4.5 procedure codes (eTable 1). Cases were divided into two groups: those with cardiovascular LEs (involving at least one cardiovascular hospitalisation occurring exclusively five or more years post diagnosis of cancer) and those without cardiovascular LEs (either no reported LEs or any cardiovascular episode prior to or within five years of cancer diagnosis (occurred in less than 1%)). Events were identified from all diagnosis and procedure fields, however, only the first occurrence of a particular event was included in the analysis so that ongoing conditions, which could be recorded multiple times, were not duplicated.

The risk of cardiovascular LEs was modelled using Royston-Parmar relative survival - adjusting for the risk of a cardiovascular event in the general population by attained age, year of event and sex (Royston & Lambert, 2006). . Explanatory variables included gender, age and year at diagnosis, diagnostic group, deprivation (Index of Multiple Deprivation, Department for Communities and Local Government (2007)) and initial treatment type. Further models were fitted to the following subgroups:

i) Cases who received chemotherapy – to examine the effect of the number of different anthracycline drugs administered (in the absence of accurate dose information).

ii) Cases who received radiotherapy (excluding cerebrovascular LEs) – to examine the effect of radiation to the chest.

Cumulative incidence for cardiovascular LEs was estimated, treating death without cardiovascular LE as a competing risk. Hospitalisation rate ratios (HRR) comparing the survivor cohort to the general population were calculated overall and by age group using standardised mortality ratio techniques, and were standardised to the general population by single year of attained age, year of event and sex (Juul, 2006).

RESULTS

Data Linkage

A total of 3,306 met the inclusion criteria and of these 98% (n=3,247) linked to at least one inpatient HES record. Outpatient records were available for 2,412 (74%) cases; however, 99% of outpatient diagnosis codes were classified as "other and unknown causes of morbidity", and were therefore not used any further.

Cardiovascular LEs

119 (3.6%) individuals had at least one cardiovascular LE (n=40 and 79 for 0–14 and 15–29 year olds respectively). The cumulative incidence was 7.5% (95%CI 5.3%-10.3%) and 14.0% (95%CI 9.9%-18.8%) for 0-14 and 15-29 year olds respectively at 20 years from diagnosis (see eFigure 1). The majority of cases experienced one cardiovascular LE (70%), 15% experienced two and the remainder experienced between 3 and 12. The median time to cardiovascular LE was 10.2 years from diagnosis (IQR = 6.8 to 13.4 years) which did not vary by type (see eFigure 2).

Comparison of cancer cohort to the general population

The crude incidence of cardiovascular LEs per 10,000 person-years was higher amongst cancer survivors than the general population (51.29 vs. 35.19) (Table 1). Amongst childhood survivors higher rates were observed for 'hypertension' (7.8 vs. 3.0), 'cardiomyopathy and heart failure' (8.4 vs. 0.9) and 'cerebrovascular disease' (5.8 vs. 0.9). For young adult survivors higher incidence was observed for 'cardiomyopathy and heart failure' (6.6 vs. 2.3) and 'pulmonary heart disease' (6.06 vs. 2.83). Overall, the rate of cardiovascular hospitalisations was higher for the childhood cohort compared to the general population (HRR = 2.6, 95% CI 1.9-3.6), but not for the young adult cohort (HRR = 1.2, 95% CI 0.9–1.5) (Figure 1). Amongst the younger cohort, there was a significant increased risk of

'cardiomyopathy and heart failure' (HRR=12.7, 95% CI 7.4-21.9), 'cerebrovascular disease' (HRR=7.9, 95% CI 4.1-15.2), 'pericardial disease' (HRR=7.9, 95% CI 3.3-19.0), 'hypertension' (HRR=4.0 95% CI 2.3-7.1), 'valvular heart disease' (HRR=3.2, 95% CI 1.0-10.0) and 'operations and procedures' (HRR=2.2, 95% CI 1.0-4.5). Despite no significant increased hospitalisation rate for young adults overall, there was a significant increase in the hospitalisation rate of 'pericardial disease' (HRR=4.0, 95% CI 1.8-8.8), 'cardiomyopathy and heart failure' (HRR=3.8, 95% CI 2.2-6.6), 'pulmonary heart disease' (HRR=3.5, 95% CI 2.0-6.4), 'conduction disorders' (HRR=2.0, 95% CI 1.2-3.2) and 'hypertension' (HRR=1.8, 95% CI 1.3-2.5) in this age group. Results for both age groups combined are given in eTable 3.

Predictors of cardiovascular LEs

There was significant evidence of an increased risk of cardiovascular LEs for those diagnosed aged 15-29 years compared to those diagnosed aged 0-14 years in the unadjusted analysis (HR=1.69, *P* value = 0.007); no further differences in demographic and clinical variables were observed (eTable 2). The excess hazard ratio of age at diagnosis in the adjusted relative survival model was 1.35; however, this effect was not significant (Table 2).

There was no significant difference in the risk of cardiovascular LEs according to the number of anthracycline drugs administered (HR=0.56; 95% CI 0.2-1.4; *P*-value=0.204). We observed borderline significant evidence of an increased the risk of cardiovascular LEs (excluding cerebrovascular disease) for those who received radiotherapy to the chest (HR=7.36; 95% CI 0.97–55.7; *P*-value=0.053) (eTables 3 and 4).

DISCUSSION

We report the first population based study, extending over 15 years, of cardiovascular LEs in survivors of childhood and young adults with cancer using person–linked electronic health records of specialist cancer registry and administrative hospital admission data. Notably, there was evidence of a significant increase in cardiovascular morbidity in survivors of childhood cancer compared with the general population, whilst within individuals diagnosed in young adulthood the increased incidence was limited to 'pericardial disease', 'cardiomyopathy and heart failure', 'pulmonary heart disease', 'conduction disorders' and 'hypertension' compared to the general population.

Treatment specific analysis showed an increase in the risk of cardiovascular LEs for those who received chest radiation which is consistent with previous studies (Mulrooney *et al*, 2009; Tukenova *et al*, 2010). However increases in the risk of cardiovascular LEs according to the use and number of anthracyclines were not observed. We did not have access to chemotherapy and radiotherapy dose information within this study; this has recently been addressed by others for survivors of childhood cancer (Blanco *et al*, 2011; Mulrooney *et al*, 2009; Tukenova *et al*, 2010; van der Pal *et al*, 2012), however, more comprehensive studies using accurate treatment data are still required. Furthermore, this line of enquiry should be extended to young adult cancer survivors in order to facilitate evidence–based risk stratification of follow–up and aftercare (Jefford *et al*, 2013).

We undertook a bespoke patient–level linkage of clinical and administrative databases to study the effect of clinical exposures on long–term cardiovascular outcomes over many thousands of patient years. However, the study depends on the quality of data coding which is likely to vary across England focus on one region may have mitigated some bias. The

inability to adequately interrogate outpatient data highlights a potential underestimation of the true size of the problem; therefore further work should concentrate on these data.

It is important that those at risk of developing cardiovascular LEs are supported with strategies to maximise cardiovascular health and given access to appropriate health surveillance. Furthermore, all of their current and potential future health carers should be made aware of the specific risks for these individuals.

ACKNOWLEDGEMENTS

Funding: This paper presents independent research commissioned by the Candlelighters Trust [Grant Reference Number RG.EPID.474842 to RGF]. AG's time was funded by Macmillan Cancer Support, Candlelighters Trust and the Yorkshire Cancer Network; the latter additionally funded the purchase HES data.

We are grateful to Paula Feltbower for data collection and the co–operation of all oncologists, pathologists, GPs and medical records staff in Yorkshire. We acknowledge to work of Rebecca Birch and colleagues at NYCRIS for their advice and support in the use of HES data, and we also acknowledge the work by the NHS Information Centre for performing the HES data linkage.

REFERENCES

Blanco JG, Sun CL, Landier W, Chen L, Esparza-Duran D, Leisenring W, Mays A, Friedman DL, Ginsberg JP, Hudson MM, Neglia JP, Oeffinger KC, Ritchey AK, Villaluna D, Relling MV, Bhatia S (2011) Anthracycline-Related Cardiomyopathy After Childhood Cancer: Role of Polymorphisms in Carbonyl Reductase Genes. *A Report From the Children's Oncology Group* **29:** 1-8

Cancer Research UK (2012) CancerStats: Teenage and Young Adult Cancer - Survival. *http://wwwcancerresearchukorg/cancer-info/cancerstats/keyfacts/teenage-and-young-adult-cancer/#survive*: Date Accessed: 23/01/2013

Department for Communities and Local Government (2007) The English Indices of Deprivation. *London; © Crown Copyright*

Hawkins MM (2010) Survivorship outcomes research based on record linkage. *Pediatr Blood Cancer* **55:** 224-225

Jefford M, Rowland J, Grunfeld E, Richards M, Maher J, Glaser A (2013) Implementing improved post-treatment care for cancer survivors in England, with reflections from Australia, Canada and the USA. *Br J Cancer* **108:** 14-20

Juul S (2006) *An introduction to Stata for health researchers*. Texas: Stata Press

Mulhern R, Merchant T, Gajjar A, Reddick W, Kun L (2004) Late neurocognitive sequelae in survivors of brain tumours in childhood. *The Lancet Oncology* **5:** 399-408

Mulrooney DA, Yeazel MW, Kawashima T, Mertens AC, Mitby P, Stovall M, Donaldson SS, Green DM, Sklar CA, Robison LL (2009) Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *Br Med J* **339:** b4606

Neglia J, Friedman D, Yasui Y, Mertens A, Hammond S, Stovall M, Donaldson S, Meadows A, Robison L (2001) Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. *JNCI* **93:** 618

Oeffinger K, Mertens A, Sklar C, Kawashima T, Hudson M, Meadows A, Friedman D, Marina N, Hobbie W, Kadan-Lottick N (2006) Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med* **355:** 1572

Royston P, Lambert PC (2006) Flexible parametric survival analysis using Stata: beyond the Cox model. *Stata Press books*

Stiller C (2007) Childhood Cancer in Britain: Incidence, Survival, Mortality. *Oxford University Press*

Travis LB, Ng A, Allan JM, Pui C, Kennedy AR, Xu X, Purdy JA, Applegate K, Yahalom J, Constine LS, Gilbert ES, Boice Jr JB (2012) Second malignant neoplasms and cardiovascular disease following radiotherapy. *J Natl Cancer Inst* **104:** 1-14

Tukenova M, Guibout C, Oberlin O, Doyon F, Mousannif A, Haddy N, Guerin S, Pacquement H, Aouba A, Hawkins M (2010) Role of Cancer Treatment in Long-Term Overall and Cardiovascular Mortality After Childhood Cancer. *J Clin Oncol* **28:** 1308

van der Pal HJH, van Dalen EC, van Delden E, van Dijk IW, Kok WE, Geskus RB, Sieswerda E, Oldenburger F, Koning CC, F.E. vL, Caron HN, Kremer LC (2012) High risk of symptomatic cardiac events in childhood cancer survivors. *J Clin Oncol* **30:** 1429-1437

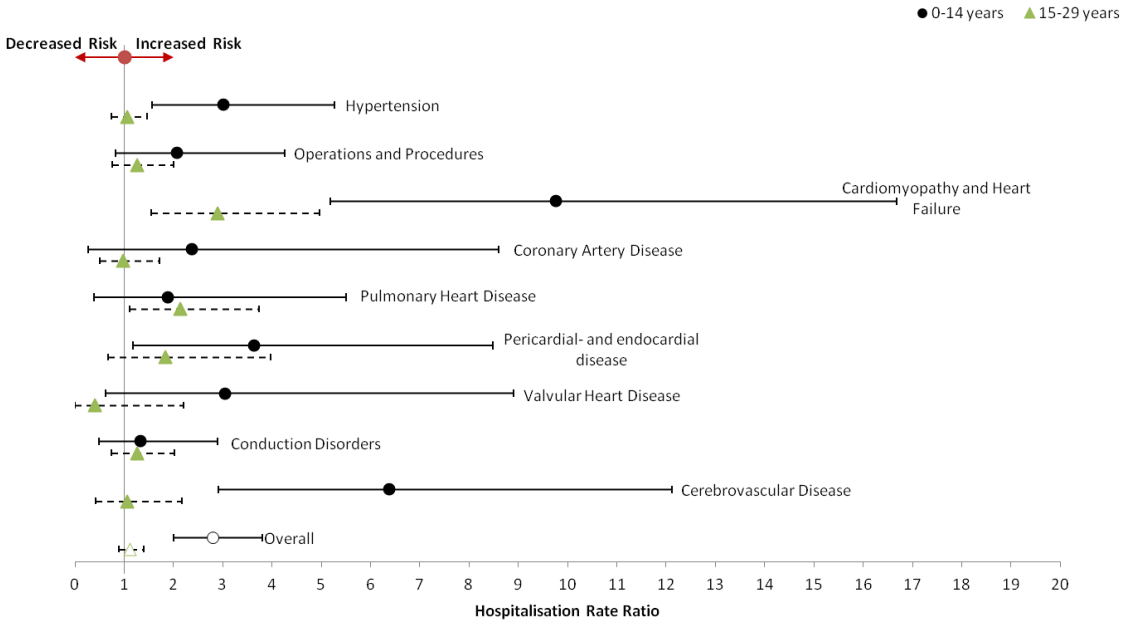
van Laar M, McKinney PA, Parslow RC, Glaser A, Kinsey SE, Lewis IJ, Picton SV, Richards M, Shenton G, Stark DP, Norman P, Feltbower RG (2010) Cancer incidence among the south Asian and non-south Asian population under 30 years of age in Yorkshire, UK. *Br J Cancer* **103:** 1448-1452

Woodward E, Jessop M, Glaser A, Stark D (2011) Late effects in survivors of teenage and young adult cancer: Does age matter? *Ann Oncol* **12:** 2561-8

Zhang Y, Lorenzi MF, Goddard K, Spinelli JJ, Gotay C, McBride ML (2013) Late morbidity leading to hospitalization among 5-year survivors of young adult cancer: A report of the childhood, adolescent, and young adult cancer survivors (CAYACS) research program. *Int J Cancer* **Advanced Online Publication.**

FIGURE LEGENDS

Figure 1: Hospitalisation rate ratios and 95% confidence intervals comparing cardiovascular late effects amongst cancer survivors to the general population by age at diagnosis



TABLES

Table 1: Number of cases[a] and crude incidence per 10,000 person-years by cardiovascular category and age group

	Age at Diagnosis[b]					
	0–14 years		15–29 years		Total	
Category	**Cancer Survivors**	**General Population**	**Cancer Survivors**	**General Population**	**Cancer Survivors**	**General Population**
	N (incidence)		N (incidence)		N (incidence)	
Hypertension	12 (7.75)	4009 (2.57)	35 (17.68)	27293 (16.80)	47 (13.32)	31580 (9.91)
Cardiomyopathy & Heart failure	13 (8.39)	1343 (0.86)	13 (6.57)	3681 (2.27)	26 (7.37)	5786 (1.82)
Operations & Procedures	7 (4.52)	3413 (2.19)	18 (9.09)	11689 (7.19)	25 (7.08)	21497 (6.75)
Conduction Disorders	6 (3.87)	4740 (3.04)	17 (8.59)	10664 (6.56)	23 (6.52)	15790 (4.96)
Cerebrovascular Disease	9 (5.81)	1479 (0.95)	7 (3.54)	5252 (3.23)	16 (4.53)	7816 (2.45)
Pulmonary Heart Disease	3 (1.94)	1606 (1.03)	12 (6.06)	4599 (2.83)	15 (4.25)	5622 (1.76)
Coronary Artery Disease	2 (1.29)	847 (0.54)	12 (6.06)	10080 (6.20)	14 (3.97)	17328 (5.44)
Pericardial Disease	5 (3.23)	1386 (0.89)	6 (3.03)	2592 (1.60)	11 (3.12)	2661 (0.84)
Valvular Heart Disease	3 (1.94)	1032 (0.66)	1 (0.51)	1986 (1.22)	4 (1.13)	4038 (1.27)
Total[c]	**60 (38.73)**	**19855 (12.71)**	**121 (61.12)**	**77836 (47.90)**	**181 (51.29)**	**112118 (35.19)**
Total Person-Years	**15492.43**	**15613297**	**19796.53**	**16246855**	**35288.96**	**31860152**

[a]For each case, multiple occurrences of the same diagnosis were not counted.

[b]Age at admission for general population corresponds to age of survivor cohort at admission dependant on their age at diagnosis.

[c]Total number of events does not equal the total number of cases as 30% of cases experienced multiple cardiovascular diagnoses.

Table 2: Excess hazard ratios (HR) and 95% confidence intervals (CI) obtained from a Royston-Parmar relative survival model, modelling the risk of a cardiovascular late event for long term survivors of cancer diagnosed between 1991 and 2006 aged 0–14 and 15–29 years inclusive.

		95% CI		
Variable	**HR**	**lower**	**upper**	***P* value**
Sex				
Male	1			
Female	1.43	0.76	2.68	0.265
Age at Diagnosis				
0–14	1			
15–29	1.35	0.67	2.71	0.391
Year of Diagnosis	1.01	0.89	1.14	0.887
Diagnostic Group				
Other solid tumours	1			
Leukaemia	1.97	0.81	4.76	0.132
Lymphoma	1.49	0.60	3.68	0.389
CNS tumours	1.55	0.56	4.28	0.394
Treatment Group				
Sx alone / No treatment recorded	1			
Cx (+/– Sx)	1.23	0.58	2.63	0.592
Rt (+/– Sx)	0.39	0.04	3.66	0.407
Cx+RT (+/– Sx)	0.92	0.34	2.54	0.880
Deprivation[a]				
Most Deprived (5)	1			
4	0.58	0.23	1.47	0.253
3	0.81	0.33	1.97	0.645
2	1.07	0.46	2.47	0.882
Least Deprived (1)	0.35	0.05	2.31	0.274

[a]Index of Multiple Deprivation 2007