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Cardiovascular sequelae in long-term survivors of young peoples' cancer: a linked cohort study

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Background: We aimed to define the incidence and risk of cardiovascular late effects (LEs) identified from inpatient hospital episode statistics (HES) among long-term survivors of cancer in young people by age at diagnosis (0–14 and 15–29 years).

Methods: Records from the Yorkshire Specialist Register of Cancer in Children and Young People (1991–2006) were linked to inpatient HES data (1996–2011) to assess rates of cardiovascular LEs. Rates were compared with the general population in Yorkshire using age–sex-matched HES records for the entire region.

Results: Of 3247 survivors of cancer, 3.6% had at least one cardiovascular LE. Overall, cardiovascular hospitalisations for the childhood cohort were threefold higher compared with 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.

Conclusions: Survivors of childhood and young adult cancer remain at increased risk of cardiovascular LEs compared with the general population.

In the United Kingdom, ~80% of children and young people diagnosed with a malignancy can be expected to become a long-term survivor (Stillier, 2007; Cancer Research UK, 2012). 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 (Neglia *et al*, 2001; Mulhern *et al*, 2004; Mulrooney *et al*, 2009; Tukenova *et al*, 2010; Blanco *et al*, 2012; Travis *et al*, 2012; van der Pal *et al*, 2012), whereas 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 (Oeffinger *et al*, 2006; Mulrooney *et al*, 2009), rather than more objective measures that may be achieved by the linkage of electronic health records (Hawkins, 2010; Zhang *et al*, 2013).

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We have linked routinely collected population-based cancer registry data with administrative hospital admissions data in order to quantify the incidence and risk of cardiovascular LEs among 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 5 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 postal code; cases were linked to outpatient HES in the same manner. Inpatient HES data were obtained for the general population resident within Yorkshire between 1996 and 2011, and were 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 and up to 5–49 years in 2011.

Statistical methods. Cardiovascular LEs were grouped as follows: hypertension, cardiomyopathy and 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 (Supplementary Table 1). Cases were divided into the following two groups: those with cardiovascular LEs (involving at least one cardiovascular hospitalisation occurring exclusively 5 or more years post diagnosis of cancer) and those without cardiovascular LEs (either no reported LEs or any cardiovascular episode before or within 5 years of cancer diagnosis (occurred in <1%)). Events were identified from all diagnosis and procedure fields within an episode; 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, thereby adjusting for the risk of a cardiovascular event in the general population by attained age, year of event and sex (Royston and 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:

- Cases who received chemotherapy – to examine the effect of the number of different anthracycline drugs administered (in the absence of accurate dose information).
- 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 (HRRs) comparing the survivor cohort with 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 3306 cases met the inclusion criteria, and of these cases 98% ($n = 3247$) linked to at least one inpatient HES record. Outpatient records were available for 2412 (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. One-hundred and nineteen (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% confidence interval (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 (Supplementary Figure 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 (Supplementary Figure 2).

Comparison of cancer cohort with the general population. The crude incidence of cardiovascular LEs per 10 000 person-years was higher among cancer survivors than the general population (51.29 vs 35.19) (Table 1). Among 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 for pulmonary heart disease (6.06 vs 2.83). Overall, the rate of cardiovascular hospitalisations was higher for the childhood cohort compared with 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). Among 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 Supplementary Figure 3.

Predictors of cardiovascular LEs. There was significant evidence of an increased risk of cardiovascular LEs for those diagnosed aged 15–29 years compared with 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 (Supplementary Table 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 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) (Supplementary Tables 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

Table 1. Number of cases^a and crude incidence per 10 000 person-years by cardiovascular category and age group

Category	Age at diagnosis ^b					
	0–14 years		15–29 years		Total	
	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)	27 293 (16.80)	47 (13.32)	31 580 (9.91)
Cardiomyopathy and heart failure	13 (8.39)	1343 (0.86)	13 (6.57)	3681 (2.27)	26 (7.37)	5786 (1.82)
Operations and procedures	7 (4.52)	3413 (2.19)	18 (9.09)	11 689 (7.19)	25 (7.08)	21 497 (6.75)
Conduction disorders	6 (3.87)	4740 (3.04)	17 (8.59)	10 664 (6.56)	23 (6.52)	15 790 (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)	10 080 (6.20)	14 (3.97)	17 328 (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)	19 855 (12.71)	121 (61.12)	77 836 (47.90)	181 (51.29)	112 118 (35.19)
Total person-years	15 492.43	15 613 297	19 796.53	16 246 855	35 288.96	31 860 152

^aFor each case, multiple occurrences of the same diagnosis were not counted.
^bAge at admission for general population corresponds to age of survivor cohort at admission dependent on their age at diagnosis.
^cTotal number of events does not equal to the total number of cases, as 30% of cases experienced multiple cardiovascular diagnoses.

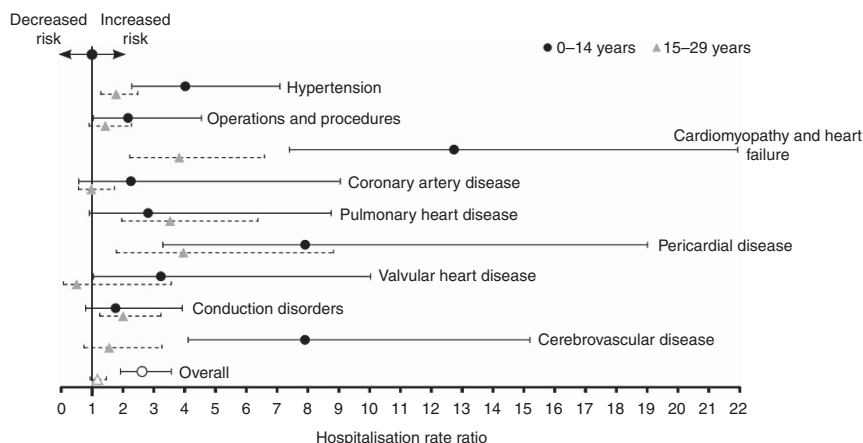


Figure 1. HRRs and 95% confidence intervals comparing cardiovascular LEs among cancer survivors with the general population by age at diagnosis.

compared with the general population, whereas 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 with 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 (Mulrooney *et al*, 2009; Tukenova *et al*, 2010; Blanco *et al*, 2012; 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, however, by focusing on one region we 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.

Table 2. Excess HRs and 95% 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

Variable	HR	95% CI		P-value
		Lower	Upper	
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				
1991–2006	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

Abbreviations: CI = confidence interval; HR = hazard ratio.
^aIndex of Multiple Deprivation 2007.

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