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Subsequent hospitalisation experience of 5-year survivors of childhood, adolescent, and young adult cancer in Scotland: a population based, retrospective cohort study

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Background: Survivors of childhood, adolescent, and young adult cancer are known to be at risk of late effects of their disease and its treatment. Most population-based studies of cancer survivors have reported on second primary cancers and mortality. The aim of this study was to research acute and psychiatric hospital admission rates and length of stay in 5-year survivors of cancer diagnosed before the age of 25 years.

Methods: This was a population-based retrospective cohort study using linked national cancer registry, acute hospital discharge, psychiatric hospital, and mortality records. The study population consisted of 5229 individuals who were diagnosed with cancer before the age of 25 years between 1981 and 2003, and who survived at least 5 years after the date of diagnosis of their primary cancer. Indirect standardisation for age and sex was used to calculate standardised bed days and hospitalisation ratios (SBDR and SHR) for both acute and psychiatric hospital admissions, and absolute excess risks (AERs) compared with the general Scottish population.

Results: Five-year survivors of cancer, diagnosed before the age of 25 years, are at increased risk of admission to acute hospitals (SHR 2.8; 95% confidence interval 2.7–2.9) and of spending more time in hospital (SBDR 3.7; 3.6–3.7). Corresponding AERs were 6.4 (6.0–6.6) admissions and 64.8 (64.4–66.9) bed days per 100 cancer survivors per year. In contrast, 5-year survivors were not at higher risk of admission to psychiatric hospital (SHR 0.9; 0.8–1.2), and they spent significantly less time as psychiatric in-patients (SBDR 0.4; 0.4–0.4) compared with the whole population.

Conclusion: Using routinely collected linked records, our population-based study has demonstrated increased rates of hospitalisation in 5-year survivors of cancer diagnosed before the age of 25 years. Long-term clinical follow-up of survivors of cancer in this age group should focus on the prevention and treatment of the late effects of cancer in those patients at highest risk of hospitalisation.

As a result of advances in treatment, around 80% of children and young people with cancer now survive at least 5 years after diagnosis. However, around two-thirds of survivors experience at least one late effect of treatment, and around a third experiences a severe or life-threatening late effect (Bhatia and Constine, 2009). Long-term complications include second primary cancers, and effects on the endocrine, cardiac and respiratory systems, renal impairment, gastrointestinal dysfunction, musculoskeletal

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sequelae, neurocognitive dysfunction, and psychosocial manifestations (Bhatia and Constine, 2009; Edgar *et al*, 2009; Mulrooney *et al*, 2009; Recklitis *et al*, 2010; Brinkman *et al*, 2013; Lund *et al*, 2013; Scottish Intercollegiate Guidelines Network, 2013; Wallace *et al*, 2013).

There have been a number of studies of late morbidity and late mortality arising in long-term survivors of childhood, adolescent, and young adult cancer. However, most of the population-based studies have focused on mortality whereas studies of morbidity have often been conducted in selected populations of patients.

We have previously described the mortality experience of a population-based cohort of 5-year survivors of childhood, adolescent, and young adult cancer originally diagnosed between 1981 and 2003 in Scotland (Brewster *et al*, 2013). The aim of the present study was to describe patterns of hospitalisation as a surrogate measure of morbidity in the same cohort of patients.

MATERIALS AND METHODS

We performed a population-based retrospective cohort study to investigate acute and psychiatric hospital admission rates and length of stay in 5-year survivors of cancer diagnosed during childhood, adolescence, or early adulthood (both for all conditions combined and for specific diagnoses). Analyses were based on a national linked database, achieved by probability matching and comprising acute hospital discharge records, psychiatric hospital records, cancer registrations, and mortality records (Kendrick and Clarke, 1993). Estimates based on clerical checking suggest that rates of false positive and false negative linkages are maintained below 1% (Kendrick, 1997). False positive and false negative links are likely to be less common nowadays because of more widespread availability and use of the Community Health Index number, a unique identifying number in Scotland. Emigrations of patients registered with cancer from Scotland to other UK countries are notified to the cancer registry by the National Health Service Central Register (NHSCR), allowing censoring of data for these individuals.

The study population comprised patients registered with the Scottish Cancer Registry who had survived at least 5 years after the diagnosis of a first cancer in childhood, adolescence, or young adulthood (age between 0 and 24 years). We included data for individuals whose year of diagnosis was in 1981 or subsequent years up to 2003.

In relation to first cancer, the study population was re-classified according to the third edition of the International Classification of Childhood Cancer (ICCC-3) (0–14 year olds) (Steliarova-Foucher *et al*, 2005) and the most up-to-date version of the diagnostic classification of cancer in adolescents and young adults developed by Birch *et al* (2002) (15–24 year olds). The data were then mapped to a common 'study classification'. As described previously (Brewster *et al*, 2013), this was based primarily on ICCC-3 but with separation of group XI (other malignant epithelial neoplasms and malignant melanomas) into two categories: (1) melanoma and skin carcinomas and (2) other carcinomas, excluding renal, hepatic, gonadal, and skin. Mapping of cancers in adolescents and young adults was based initially on specific morphology codes (sometimes in combination with topography codes); thereafter, the mapping was based on groups and subgroups within the Birch *et al* classification (see Appendix 1).

As an indicator of socio-economic position, based on postcode sectors of residence at the time of original diagnosis, individuals were assigned to fifths of Carstairs deprivation scores by applying 1981, 1991, and 2001 census-derived Carstairs scores to the periods of diagnosis 1981–1985, 1986–1995, 1996–2003, respectively. The Carstairs deprivation index is based on the small area of residence, and is derived from four variables collected at each decennial census: social class, unemployment, overcrowding, and car ownership (Morris and Carstairs, 1991).

Four main analyses defined by four main end points of interest were carried out, focussing on (1) the total number of bed days spent in acute hospitals; (2) incident cases of non-psychiatric disease-specific morbidity as defined by first ever admission to acute hospitals with particular diagnoses; (3) the total number of bed days spent in psychiatric hospitals; and (4) incident cases of psychiatric disease-specific morbidity as defined by first ever admission to psychiatric hospital with particular diagnoses. Indirectly standardised bed days ratios (SBDRs) and hospitalisation ratios (SHRs) were calculated for all diagnoses combined (SBDR and SHR) and for specific diagnoses (SHR only—see Appendix 2), using the general population as an external comparison group to generate expected numbers of bed days/admissions (based on age-, sex-, deprivation category-, and calendar period-specific rates of in-patient bed days or disease-specific admissions). For SBDRs, follow-up was from 5 years after diagnosis to date of emigration, date of death, or end of 2009, whichever occurred first. For SHRs, follow-up was from 5 years after diagnosis to date of first hospital admission (for a relevant diagnosis), date of emigration, date of death, or end of 2009, whichever occurred first. Absolute excess risks (AERs) were calculated as the observed minus the expected number of bed days or hospital admissions divided by the number of person-years at risk and expressed as the rate per 100 cancer survivors per year. In this context, the AER reflects the additional burden of hospitalisation beyond background levels. 95% confidence intervals around SBDRs, SHRs, and AERs were calculated based on the assumption that the observed numbers of bed days/admissions followed a Poisson distribution. Standardised bed days ratios and SHRs with 95% confidence intervals that did not include the value 1.0 were regarded as statistically significantly different from those observed in the general population. Cumulative incidence was estimated using the Kaplan–Meier method, and differences in cumulative incidence according to socio-economic position were assessed for statistical significance using the log-rank test.

RESULTS

From an original cohort of 6980 children and young people diagnosed with cancer in Scotland between 1981 and 2003, the study population comprised 5229 individuals who had survived for at least 5 years after the date of diagnosis of their primary cancer. Overall, beyond the point of 5-year survival, they contributed 58 359 person-years of follow-up for the SBDR analyses, and 31 214 and 57 769 person-years of follow-up for the SHR analyses of acute hospital admissions and psychiatric hospital admissions, respectively.

In general, SBDRs (and SHRs) were little altered by standardisation for deprivation. For the sake of comparability with other studies, the results presented here are standardised for age and sex only. Overall, the study population experienced 52 295 in-patient bed days in acute hospitals, yielding an SBDR of 3.7 (95% confidence interval 3.6–3.7). This corresponds to an AER of 64.8 (64.4–66.9) in-patient bed days per 100 cancer survivors per year (observed rate 89.6 and expected rate 24.8). Standardised bed days ratios were higher in patients whose cancer was diagnosed at a young age and in patients from deprived areas of residence; they decreased with increasing follow-up time; and they varied substantially by type of primary cancer, ranging from 1.3 (1.2–1.3) in patients originally diagnosed with melanoma and skin carcinomas to 11.4 (10.2–12.7) in patients originally diagnosed with hepatic tumours (Table 1).

Table 1. Characteristics of the study population of 5-year survivors of cancers diagnosed under 25 years of age in Scotland 1981–2003, observed number of in-patient bed days beyond 5 years after their first cancer diagnosis, indirectly standardised bed days ratio (SBDR), and 95% confidence intervals (based on acute hospital discharge data and psychiatric hospitalisation data)

			Acute hospitalisations				Psychiatric hospitalisations			
					95% CI				95% CI	
Characteristic	Number of patients	%	Observed bed days	SBDR	LCI	UCI	Observed bed days	SBDR	LCI	UCI
All patients combined	5229	100	52 295	3.7	3.6	3.7	5631	0.4	0.4	0.4
Age at diagnosis of first cancer (years)										
<1	188	3.6	3203	10.6	10.3	11.0	0	0.0	—	—
1–4	802	15.3	7495	5.1	5.0	5.3	761	1.0	0.9	1.0
5–9	555	10.6	6851	6.3	6.1	6.4	374	0.4	0.4	0.5
10–14	631	12.1	6759	4.7	4.6	4.8	1572	1.0	0.9	1.0
15–19	1043	19.9	10 748	3.5	3.4	3.6	908	0.3	0.2	0.3
20–24	2010	38.4	17 239	2.4	2.4	2.5	2016	0.3	0.3	0.3
Sex										
Male	2762	52.8	26 937	3.5	3.5	3.6	2887	0.3	0.3	0.3
Female	2467	47.2	25 358	3.7	3.7	3.8	2744	0.6	0.5	0.6
Carstairs deprivation fifth										
1—Least deprived	1087	20.8	9220	3.0	3.0	3.1	1499	0.5	0.5	0.5
2	1005	19.2	11 050	3.8	3.8	3.9	1203	0.4	0.4	0.5
3	1040	19.9	10 722	3.7	3.7	3.8	1221	0.4	0.4	0.5
4	1055	20.2	10 123	3.5	3.4	3.6	783	0.3	0.3	0.3
5—Most deprived	1036	19.8	11 170	4.1	4.0	4.2	925	0.3	0.3	0.4
Follow-up time (years)										
⩾5, <10	1195	22.9	11 816	20.1	19.8	20.5	137	0.3	0.3	0.4
⩾10, <15	1242	23.8	10 309	5.7	5.6	5.9	1065	0.7	0.6	0.7
⩾15, <20	1162	22.2	10 711	3.4	3.3	3.4	1921	0.6	0.6	0.6
⩾20	1630	31.2	19 459	2.2	2.2	2.3	2508	0.3	0.3	0.3
Type of first cancer										
Leukaemias	884	16.9	11 034	6.3	6.2	6.4	1176	0.8	0.8	0.9
Lymphomas	980	18.7	8775	2.8	2.8	2.9	571	0.2	0.2	0.2
CNS tumours	587	11.2	10 783	7.9	7.8	8.1	1678	1.3	1.2	1.3
Neuroblastoma	93	1.8	903	5.2	4.9	5.6	0	0.0	—	—
Retinoblastoma	81	1.5	825	4.7	4.4	5.0	0	0.0	—	—
Renal tumours	154	2.9	1811	5.8	5.6	6.1	456	2.3	2.1	2.5
Hepatic tumours	19	0.4	339	11.4	10.2	12.7	0	0.0	—	—
Bone tumours	188	3.6	2216	4.6	4.4	4.8	194	0.4	0.3	0.4
Soft tissue sarcomas	317	6.1	3311	4.1	4.0	4.3	46	0.1	0.0	0.1
Germ cell tumours	694	13.3	4495	1.9	1.9	2.0	386	0.1	0.1	0.2
Melanoma and skin carcinomas	709	13.6	2593	1.3	1.2	1.3	313	0.2	0.1	0.2
Other carcinomas	459	8.8	3480	2.2	2.1	2.3	418	0.3	0.3	0.3
Other and unspecified neoplasms	64	1.2	1730	5.6	5.3	5.8	393	1.3	1.2	1.5

Abbreviations: CI = confidence interval; LCI/UCI = lower/upper 95% confidence interval.

Table 2 shows, for selected primary cancers, SHRs for broad diagnostic categories based on the acute hospital discharge data. For all primary cancers combined, and for all subsequent diagnoses combined, the SHR was 2.8 (2.7–2.9), corresponding to an AER of 6.4 (6.0–6.6) hospital admissions per 100 cancer survivors per year (observed rate 9.9 and expected rate 3.5). Standardised hospitalisation ratios were significantly increased for most diagnostic categories, including neoplasms (disease recurrences and subsequent primaries combined). Of particular note, high SHRs are seen for endocrine disease (including diabetes mellitus) in patients with a history of leukaemia or CNS tumours; for diseases of the nervous system in patients with CNS tumours, leukaemia, or soft tissue sarcomas; for diseases of the circulatory system in patients with leukaemia and bone tumours (as well as specifically cardiomyopathy following leukaemia and soft tissue sarcoma, and cerebrovascular disease following leukaemia and CNS tumours); for diseases of the respiratory system in patients with leukaemia; for congenital malformations in patients with CNS tumours and soft tissue sarcoma; and for external causes in patients with bone tumours.

Figures 1 and 2 show, respectively, for all 5-year survivors, the cumulative incidence of diseases of the respiratory system and external causes of morbidity and mortality by deprivation fifth. The cumulative incidence of both of these broad categories of

Table 2. Standardised hospitalisation ratios (SHR) among 5-year survivors of childhood, adolescent, or young adult cancer (based on acute hospital discharge data)

	Primary cancer																							
	All cancers				Leukaemia				Lymphoma				CNS				Bone				Soft tissue sarcoma			
			95% CI				95% CI				95% CI				95% CI				95% CI				95% CI	
Subsequent diagnoses	**O**	**SHR**	**LCI**	**UCI**	**O**	**SHR**	**LCI**	**UCI**	**O**	**SHR**	**LCI**	**UCI**	**O**	**SHR**	**LCI**	**UCI**	**O**	**SHR**	**LCI**	**UCI**	**O**	**SHR**	**LCI**	**UCI**
All diagnoses combined	3075	2.8	2.7	2.9	547	3.9	3.6	4.3	562	2.4	2.2	2.7	413	4.5	4.0	4.9	127	3.8	3.2	4.5	191	3.0	2.6	3.5
Certain infectious and parasitic diseases	380	2.2	2.0	2.5	112	4.6	3.8	5.6	92	2.7	2.2	3.3	44	2.4	1.7	3.2	13	2.2	1.2	3.8	18	1.7	1.0	2.7
Neoplasms	1252	8.1	7.7	8.6	288	21.0	18.6	23.6	221	6.6	5.8	7.5	211	16.9	14.7	19.3	51	10.3	7.6	13.5	92	11.6	9.4	14.2
Endocrine, nutritional, and metabolic diseases	408	4.3	3.8	4.7	108	10.9	9.0	13.2	72	3.5	2.7	4.4	84	10.7	8.6	13.3	12	4.0	2.1	6.9	17	3.3	1.9	5.3
Diabetes mellitus	51	1.6	1.2	2.1	12	3.1	1.6	5.4	10	1.5	0.7	2.7	8	2.8	1.2	5.5	1	1.0	0.0	5.4	3	1.8	0.4	5.2
Diseases of the nervous system	353	2.9	2.6	3.2	43	3.1	2.2	4.1	39	1.5	1.0	2.0	149	15.5	13.2	18.3	8	2.0	0.9	3.9	21	3.1	1.9	4.8
Diseases of the circulatory system	361	1.7	1.5	1.9	51	2.7	2.0	3.5	83	1.7	1.4	2.1	35	2.0	1.4	2.8	19	2.7	1.6	4.2	15	1.4	0.8	2.3
Coronary heart disease	28	1.4	1.0	2.1	1	1.2	0.0	6.7	18	3.6	2.1	5.6	0	0.0		3.4	0	0.0		6.3	0	0.0		5.7
Cardiomyopathy	13	5.3	2.8	9.0	7	32.4	13.0	66.7	2	3.4	0.4	12.2	0	0.0		18.7	1	12.4	0.3	69.2	2	17.8	2.2	64.2
Cerebrovascular disease	36	2.6	1.8	3.5	7	6.7	2.7	13.7	3	0.9	0.2	2.6	12	11.9	6.2	20.8	0	0.0		8.0	2	3.2	0.4	11.4
Diseases of the respiratory system	583	1.7	1.6	1.9	124	2.3	1.9	2.7	119	1.9	1.5	2.2	80	2.1	1.7	2.6	23	2.1	1.3	3.2	38	1.8	1.3	2.5
Diseases of the digestive system	964	1.6	1.5	1.8	203	2.6	2.2	2.9	186	1.6	1.4	1.8	101	1.7	1.4	2.1	29	1.5	1.0	2.2	57	1.6	1.2	2.1
Diseases of the genitourinary system	623	1.5	1.4	1.7	90	1.9	1.5	2.3	112	1.3	1.1	1.6	59	1.6	1.2	2.0	21	1.6	1.0	2.4	39	1.7	1.2	2.3
Congenital malformations, deformations and chromosomal abnormalities	173	3.1	2.7	3.7	32	2.8	1.9	4.0	10	1.1	0.5	2.0	41	6.4	4.6	8.7	4	2.7	0.7	6.9	31	8.5	5.8	12.0
Injury, poisoning and certain other consequences of external causes	793	1.3	1.3	1.4	145	1.4	1.2	1.7	149	1.3	1.1	1.5	131	2.1	1.7	2.4	45	2.4	1.8	3.2	44	1.1	0.8	1.5
External causes of morbidity and mortality	849	1.6	1.5	1.7	151	1.6	1.3	1.9	162	1.5	1.3	1.8	138	2.4	2.0	2.9	48	2.8	2.1	3.7	52	1.5	1.1	2.0
Suicide, intentional self-harm and undetermined intent	124	4.3	3.6	5.2	8	1.7	0.7	3.3	27	4.8	3.1	6.9	14	4.2	2.3	7.0	8	7.9	3.4	15.5	5	2.7	0.9	6.4
Accidental poisoning	24	0.1	0.0	0.1	3	0.0	0.0	0.1	9	0.1	0.1	0.2	2	0.0	0.0	0.2	0	0.0		0.3	0	0.0		0.1
All other accidents	498	0.4	0.4	0.5	85	0.5	0.4	0.7	103	0.4	0.4	0.5	80	0.7	0.6	0.9	19	0.5	0.3	0.8	34	0.5	0.4	0.7
Other causes	1613	1.7	1.6	1.8	265	2.1	1.9	2.4	277	1.4	1.2	1.5	230	2.6	2.3	2.9	69	2.3	1.8	2.9	89	1.5	1.2	1.9

Abbreviations: LCI/UCI = lower/upper 95% confidence interval; O = observed numbers of cases; SHR = standardised hospitalisation ratio.

disease was significantly higher among the most compared with the least deprived fifth of the population ($P<0.001$) with divergence over time.

In relation to psychiatric hospitalisation, the study cohort experienced 5631 bed days, corresponding to an SBDR of 0.4 (0.4–0.4). Although lower than expected compared with the Scottish population, SBDRs were higher in females than in males, in patients from less deprived areas of residence, and during the second decade of follow-up. They were higher than expected in patients originally diagnosed with CNS tumours (1.3, 1.2–1.3), renal tumours (2.3, 2.1–2.5), and other and unspecified neoplasms (1.3, 1.2–1.5) (Table 1).

Table 3 shows, for all primary cancers combined and for CNS tumours, SHRs for broad diagnostic categories based on the

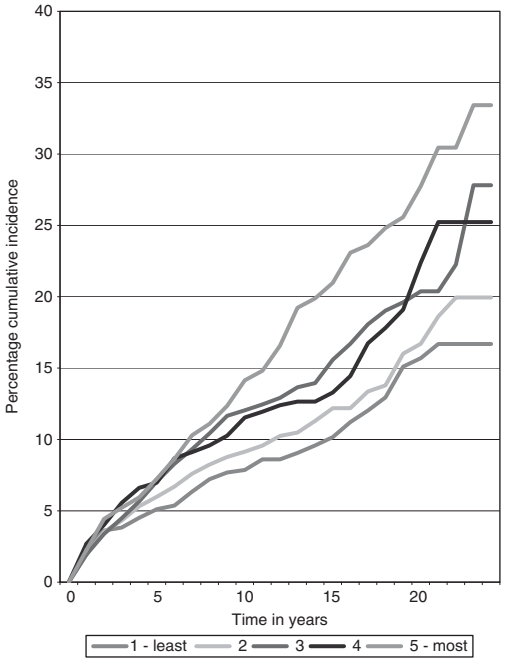

Figure 1. Cumulative incidence of diseases of the respiratory system (ICD-10 J00–J99) among survivors from date of 5-year survival, by deprivation fifth.

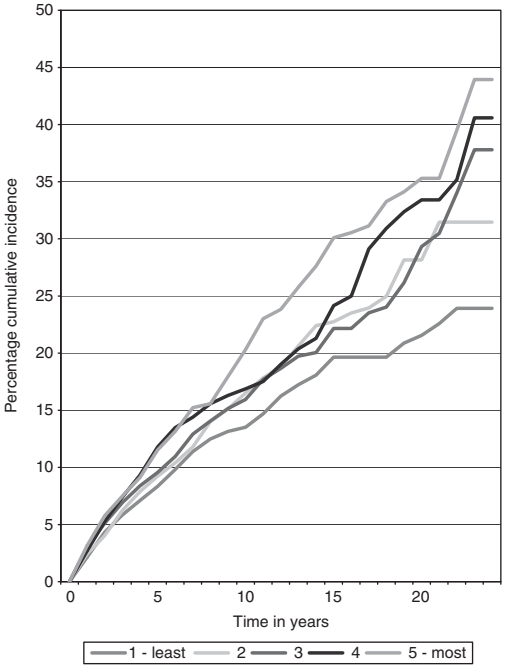

Figure 2. Cumulative incidence of external causes of morbidity and mortality (ICD-10 V01–Y98) among survivors from date of 5-year survival, by deprivation fifth.

psychiatric hospitalisation data. For all primary cancers combined, and for all subsequent diagnoses combined, the SHR was 0.9 (0.8–1.2). Overall, there were no significantly increased SHRs for any category of mental illness diagnostic group recorded during hospitalisation. However, for patients with a history of CNS tumours, higher than expected SHRs were seen for organic mental disorders, such as 'subacute confusional state' (12.8, 3.5–32.6).

DISCUSSION

We have shown that 5-year survivors of cancer diagnosed before the age of 25 years remain at increased risk of admission to acute hospitals and of spending more time in hospital than the general population of similar age and sex. However, the AER of hospital admission is low, reflecting relatively low background risks of hospitalisation among young people. Increased risks of hospitalisation with specific conditions are largely consistent with established late effects of cancer and its treatment (Scottish Intercollegiate Guidelines Network, 2013; Wallace *et al*, 2013). The risk of spending time in hospital seems particularly high among survivors of cancer diagnosed at a very young age. This may reflect the patterns of cancers diagnosed in this age group, which determines the intensity of therapy and its impact on child growth and development. In contrast, members of our study population were not at higher risk of admission to psychiatric hospital, and they spent significantly less time as psychiatric in-patients than the population as a whole. However, patients with a history of CNS tumours spent more time than expected in psychiatric hospital.

Our study has a number of strengths. In Scotland, the National Health Service (NHS) is funded by taxation and free at the point of use. The absence of barriers to treatment, such as charges, means that we expect to have identified most hospital in-patient-related morbidity from routinely collected data. Thus, while our study focuses on the more severe end of the spectrum of diseases leading to hospitalisation, it can nevertheless be regarded as effectively population based. As such, it is not subject to some of the biases associated with self-reporting (Taylor *et al*, 2010), non-participation (Mulrooney *et al*, 2009), and studies from specialist centres (Ness *et al*, 2009).

Scottish Cancer Registry data have been shown to be of comparatively high quality (Brewster *et al*, 1997, 2002) and record linkage between routinely collected NHS and mortality records is believed to be highly accurate and complete (Kendrick and Clarke, 1993; Kendrick, 1997). Hospitalisation data are supported by an active programme of quality assurance including regular assessments of data quality. In relation to discharges from acute hospitals, the accuracy of coding of main diagnosis has been estimated to be around 88% overall and has been relatively stable for around 20 years (Information Services Division, 2012).

Compared with analyses using mortality data, hospitalisation data yield more events occurring sooner (for example, during follow-up, there were 13 incident cases of cardiomyopathy compared with only two deaths). Unlike many other studies, it was possible to standardise our analyses for socio-economic deprivation at the time of cancer diagnosis, although this made little difference to the results. This could reflect limitations of the area-based indicator of deprivation that we used (Morris and Carstairs, 1991).

Our study also has a number of limitations. The fact that the outcomes assessed are based on hospitalisation means that we have not been able to identify and quantify less serious morbidity which may nevertheless be important to patients (Taylor *et al*, 2010). Admissions to private hospitals will not have been captured, although the use of private health services by the age group being studied is very low. The absence of comprehensive information on cancer treatment means that it is not possible to associate specific sequelae with specific modalities of therapy. Our study population and duration of follow-up are smaller than in some other studies, which limit the capacity to carry out subgroup analyses. At the same time, the application of multiple tests of statistical

Table 3. Standardised hospitalisation ratios (SHRs) among 5-year survivors of childhood, adolescent, or young adult cancer (based on psychiatric hospitalisation data)

	Primary cancer							
	All cancers				CNS			
			95% CI				95% CI	
Psychiatric diagnosis	O	SHR	LCI	UCI	O	SHR	LCI	UCI
Mental and behavioural disorders (All diagnoses)	87	0.9	0.8	1.2	12	1.3	0.7	2.3
Organic, including symptomatic mental disorders	7	1.9	0.8	3.8	4	12.8	3.5	32.6
Mental and behavioural disorders due to psychoactive substance use	30	0.7	0.5	1.1	2	0.5	0.1	1.9
Schizophrenia, schizotypal and delusional disorders	25	1.1	0.7	1.6	6	2.5	0.9	5.5
Mood (affective) disorders	36	0.8	0.6	1.2	4	1.0	0.3	2.6
Neurotic, stress-related and somatoform disorders	18	0.8	0.5	1.2	1	0.5	0.0	2.5
Behavioural syndromes associated with physiological disturbances and physical factors	1	0.3	0.0	1.7	0	0.0	—	—
Disorders of adult personality and behaviour	7	0.6	0.2	1.2	0	0.0	—	—
Mental retardation	4	0.6	0.2	1.4	2	3.0	0.4	10.7
Disorders of psychological development	1	0.8	0.0	4.2	0	0.0	—	—
Behavioural and emotional disorders with onset usually occurring in childhood and adolescence	0	0.0	—	—	0	0.0	—	—
Unspecified mental disorder	0	0.0	—	—	0	0.0	—	—

Abbreviations: CI = confidence interval; CNS = central nervous system; LCI/UCI = lower/upper 95% confidence interval; O = observed numbers of cases.

significance has increased the risk of a type I error (spurious statistically significant findings). Finally, some members of the cohort may have emigrated from Scotland without this being recorded and are therefore lost to follow-up, but we believe that the proportion of unrecorded emigrations from the cohort is low.

We are only aware of one study (in British Columbia) that has used non-psychiatric hospitalisation data to investigate late effects of cancer in early life (Bradley *et al*, 2010; McBride *et al*, 2010; Lorenzi *et al*, 2011), although a similar study is planned in England (Hawkins, 2010). The British Columbia study has shown higher rates of hospitalisation among survivors of cancer diagnosed below the age of 20 years (Bradley *et al*, 2010), with risks varying by type of primary cancer, but highest subsequent risks for neoplasms (including second primary cancers) (Lorenzi *et al*, 2011). Although the US Childhood Cancer Survivor Study cohort has also reported higher than expected hospitalisation rates, their results were based on the self-reported data and were subject to incomplete participation (Kurt *et al*, 2012).

We are only aware of a single study (in Denmark) that used cancer registration data linked to routine psychiatric hospitalisation data to investigate psychiatric hospitalisations among survivors of cancer in childhood or adolescence (Ross *et al*, 2003). The authors found no evidence of an increased risk of admission except among survivors of brain tumours, which is consistent, in part, with our own findings. However, a recent update of the Danish study showed an increased risk of hospital contact for mental disorders, especially in children younger than 10 years at diagnosis, and in survivors of CNS tumours, haematological malignancies, and solid tumours (Lund *et al*, 2013). Despite these findings, the fact that psychosocial sequelae of childhood cancer are well recognised (Recklitis *et al*, 2010; Brinkman *et al*, 2013), and that antidepressant use has been shown to be higher among survivors of childhood, adolescent, and young adult cancer in British Columbia (Deyell *et al*, 2013), our data suggest an overall lower risk of serious psychiatric morbidity leading to in-patient admissions. This may reflect an inadequate period of follow-up, or it may indicate that survivors of cancer at a young age develop resilience and a degree of resistance to serious mental illness. At the same time, the SHR for all mental and behavioural disorders combined was not significantly lower than expected, suggesting that the lower SBDR is a reflection of case mix.

In relation to some of our specific findings, the increased risk of neoplasms was expected, especially as this category included admissions for recurrence of the originally diagnosed cancer, as well as for subsequent independent primary cancers. Recurrent disease accounts for part of the total burden of hospitalisations for cancer survivors, whereas at least a proportion of new primary cancers are likely to represent late effects of treatment.

An increased risk of subsequent diabetes mellitus has been associated previously with total body irradiation, abdominal irradiation, cranial irradiation (though not after adjustment in a multivariable model), use of alkylating agents, and younger age at diagnosis (Meacham *et al*, 2009). Although diabetes is known to be poorly recorded in hospital admission data for adults (Anwar *et al*, 2011), we think it highly unlikely that differential completeness of reporting between cohort members and the general population would have influenced our finding of higher ratios for hospitalisation with diabetes among cancer survivors than among the general population.

The cardiotoxic effects of radiation therapy to the chest and some chemotherapy agents are well established (van der Pal *et al*, 2012; Lipshultz *et al*, 2013). The particularly high SHRs for cardiomyopathy that we found in survivors of leukaemia and soft tissue sarcoma seem most likely to be related to past exposure to anthracycline-based therapy.

Although, in our acute hospitalisation analysis, the overall SHR for suicide, intentional self-harm, and undetermined intent is significantly higher than expected (4.3, 95% confidence interval 3.6–5.2), in our previously published analysis of mortality data, the standardised mortality ratio for suicide was not significantly increased (SMR 1.1, 95% confidence interval 0.6–2.0) (Brewster *et al*, 2013). These findings are consistent with other studies. For example, in a

recent study based on the US Childhood Cancer Survivor Study cohort, adult survivors were found to be significantly more likely to have suicide ideation than a group of non-cancer controls. Suicide ideation was strongly associated with survivors' physical health, even many years after the completion of therapy and when the effects of cancer diagnosis, treatment, and depression had been taken into account (Recklitis *et al*, 2010). In contrast, the majority of large, population-based studies have not shown an increased risk of death by suicide among survivors of childhood cancer (Hawkins *et al*, 2007).

Associations between congenital anomalies and/or genetic factors and childhood cancer have been established in many studies (Little, 1999). Specific associations include Li-Fraumeni syndrome and soft tissue sarcoma, CNS tumours, leukaemia, osteosarcoma, and adrenocortical carcinoma. In addition, neurofibromatosis has been associated with CNS tumours (although note that neurofibromatosis was classified as a neoplasm of uncertain behaviour in ICD-9; not until the introduction of ICD-10 (April 1996 for hospital data in Scotland) was it classified under congenital malformations). Although we found increased risks of hospitalisation with congenital malformations in all patients and especially those with a history of leukaemia, CNS tumours, and soft tissue sarcoma, it is important to bear in mind that some abnormalities could be secondary to the cancer (for example, hydrocephalus due to brain tumour).

Widening socio-economic inequalities in cumulative incidence of admissions for respiratory diseases and external causes may reflect, respectively, socio-economic patterning of smoking prevalence (Austin *et al*, 2005; Scottish Public Health Observatory, 2009) and of intentional self-harm and injuries of undetermined intent (Leyland *et al*, 2007) among young people that are already well recognised.

In summary, our study has shown that long-term survivors of cancer in childhood and young adulthood are at higher risk of subsequent admission to acute hospitals, but not psychiatric hospitals, compared with the general population. However, the absolute risk of admission to acute hospitals is low. Our study has also demonstrated the utility of routinely collected, linked hospitalisation records for high level monitoring of many serious, though not necessarily fatal late effects at a relatively low cost. Long-term clinical follow-up of survivors of childhood cancer should focus on the prevention and treatment of the late effects of cancer in those patients at highest risk of hospitalisation (Wallace *et al*, 2001; Edgar *et al*, 2013). Late effects related to treatment for cancer may occur soon after treatment is completed, or may not become apparent for many years or decades. Lifelong follow-up of survivors is recommended as a current best practice (Scottish Intercollegiate Guidelines Network, 2013; Wallace *et al*, 2013) and this will necessitate multidisciplinary collaboration between patients and their families, oncologists and other health professionals, including those in primary care to ensure early diagnosis, counselling and, where possible, timely initiation of appropriate treatments.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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APPENDIX 1

Study Classification of Primary Neoplasm and Mappings from ICCC-3 and Teenagers and Young Adults with Cancer (TYAC) Classifications

Table A1: Study classification of primary neoplasm

Study classification
Leukaemias
Lymphomas
CNS tumours
Neuroblastoma
Retinoblastoma
Renal tumours
Hepatic tumours
Bone tumours
Soft tissue sarcomas
Germ cell tumours
Melanoma and skin carcinomas
Other carcinomas*
Other and unspecified neoplasms

*Except renal, hepatic, gonadal, and skin.

Table A2: Mapping of Childhood Cancer Classification (ICCC-3) to Study Classification

ICCC-3 classification	Study classification
Group I—Leukaemias, myeloproliferative diseases, and myelodysplastic diseases	All Group I = Leukaemias
Group II—Lymphomas and reticuloendothelial neoplasms	All Group II = Lymphomas
Group III—CNS and miscellaneous intracranial and intraspinal neoplasms	All Group III = CNS tumours
Group IV—Neuroblastoma and other peripheral nervous cell tumours	All Group IV = Neuroblastoma
Group V—Retinoblastoma	All Group V = Retinoblastoma
Group VI—Renal tumours	All Group VI = Renal tumours
Group VII—Hepatic tumours	All Group VII = Hepatic tumours
Group VIII—Malignant bone tumours	All Group VIII = Bone tumours
Group IX—Soft tissue and other extraosseous sarcomas	All Group IX = Soft tissue sarcomas
Group X—Germ cell tumours, trophoblastic tumours, and neoplasms of gonads	All Group X = Germ cell tumours
Group XI—Other malignant epithelial neoplasms and malignant melanomas	Category XId = Melanoma and skin carcinomas Category XIe = Melanoma and skin carcinomas Remainder = Other carcinomas
Group XII—Other and unspecified malignant neoplasms	All Group XII = Other and unspecified neoplasms

Table A3: Mapping of TYAC Classification to Study Classification*

TYAC classification	Study classification
Group 1—Leukaemia	All Group 1 = Leukaemias
Group 2—Lymphoma	All Group 2 = Lymphomas
Group 3—Central nervous system and other intracranial and intraspinal neoplasms (CNS tumours)	All Group 3 = CNS tumours

(Continued)

TYAC classification	Study classification
Group 4—Osseous and Chondromatous Neoplasms, Ewing tumour and other Neoplasms of Bone (Bone Tumours)	All Group 4 = Bone tumours
Group 5—Soft tissue sarcomas (STS)	All Group 5 = Soft tissue sarcomas
Group 6—Germ cell and trophoblastic neoplasms (Germ cell tumours)	All Group 6 = Germ cell tumours
Group 7—Melanoma and skin carcinoma	All Group 7 = Melanoma and skin carcinomas
Group 8—Carcinomas (except of skin)	Category 8.5.1 = Renal tumours Category 8.5.3 = Germ cell tumours Category 8.6.3 = Hepatic tumours Remainder of Group 8 = Other carcinomas
Group 9—Miscellaneous specified neoplasms NEC (Miscellaneous specified)	Category 9.1.1 = Renal tumours Category 9.1.2 = Neuroblastoma Category 9.2.1 = Neuroblastoma Category 9.2.2 = Germ cell tumours Category 9.2.3 = Lymphomas Remainder of Group 9 = Other and unspecified neoplasms
Group 10—Unspecified malignant neoplasms NEC (Unspecified)	All Group 10 = Other and unspecified neoplasms

*Any cases with ICDO morphology codes 9510/3–9514/3 = Retinoblastoma.
*Any cases with ICDO morphology codes 8970/3 = Hepatic tumours.
*Any cases with ICDO morphology codes 8964/3 = Renal tumours.
*Any cases with ICDO morphology codes 8963/3 + ICD9 189.0 or ICD10 C64 = Renal tumours.
*Any remaining cases with ICDO morphology codes 8963/3 = Soft tissue sarcomas.
*Any cases with ICDO morphology codes 9501–9504 + ICD9 191–192, 237.5, 237.6, 237.9 or ICD10 C70.0–C72.9, D32–D33, D42–D43 = CNS tumours.
*Any remaining cases with ICDO morphology codes 9501/3–9504/3 = Neuroblastoma.
*Any cases with ICDO morphology codes 9505–9508 = CNS tumours.
*Any cases with ICDO morphology codes 9520/3–9523/3 = Neuroblastoma.

APPENDIX 2

Table A4: Disease-specific outcome codes from acute hospital discharge records (first occurrence, any mention)

Disease grouping	ICD9	ICD10
Certain infectious and parasitic diseases	001–139	A00–B99
Neoplasms	140–239	C00–D48
Endocrine, nutritional and metabolic diseases	240–279	E00–E90
Diabetes mellitus	250	E10–E14
Diseases of the nervous system	320–359	G00–G99 excluding G45–G46
Diseases of the circulatory system	390–459	I00–I99, G45–G46
Coronary heart disease	410–414	I20–I25
Cardiomyopathy	425	I25.5, I41.2, I42, I43
Cerebrovascular disease	430–438	I60–I69, G45–G46

(Continued)

Disease grouping	ICD9	ICD10
Diseases of the respiratory system	460–519	J00–J99
Interstitial pneumonitis and/or pulmonary fibrosis caused by radiation or drugs	508	J70
Diseases of the digestive system	520–579	K00–K93
Diseases of the genitourinary system	580–629	N00–N99
Congenital malformations, deformations and chromosomal abnormalities	740–759	Q00–Q99
Injury, poisoning and certain other consequences of external causes	800–999	S00–T98
External causes of morbidity and mortality	E800–E999	V01–Y98
Suicide, intentional self-harm and injuries/events of undetermined intent	E950–E959, E980–E989	X60–X84, Y87.0, Y10–Y34, Y87.2
Accidental poisoning	E850–E869	X40–X49
All other accidents	E800–E849, E870–E949	V01–V99, W00–W99, X00–X39, X50–X59, Y40–Y59, Y85, Y86
Other causes		

Table A5: Disease-specific outcome codes from psychiatric hospitalisation records (first occurrence, any mention)

Disease grouping	ICD10	ICD9
Mental and behavioural disorders (All diagnoses)	F00–F99	290–319
Organic, including symptomatic mental disorders	F00–F09	290, 293, 294, 310
Mental and behavioural disorders due to psychoactive substance use	F10–F19	291, 292, 303, 304, 305.0, 305.1, 305.2, 305.3, 305.4, 305.5, 305.6, 305.7
Schizophrenia, schizotypal and delusional disorders	F20–F29	295, 297, 298.3, 298.4, 298.9
Mood (affective) disorders	F30–F39	296, 298.0, 298.1, 300.4, 301.1, 311
Neurotic, stress-related and somatoform disorders	F40–F48	298.2, 298.8, 300.0, 300.1, 300.2, 300.3, 300.5, 300.6, 300.7, 300.8, 300.9, 306, 307.8, 308, 309
Behavioural syndromes associated with physiological disturbances and physical factors	F50–F59	302.7, 305.8, 305.9, 307.1, 307.4, 307.5, 316
Disorders of adult personality and behaviour	F60-F69	301.0, 301.2, 301.3, 301.4, 301.5, 301.6, 301.7, 301.8, 301.9, 302.1, 302.2, 302.3, 302.4, 302.5, 302.6, 302.8, 302.9, 312.2
Mental retardation	F70–F79	317, 318, 319
Disorders of psychological development	F80–F89	299, 315
Behavioural and emotional disorders with onset usually occurring in childhood and adolescence	F90-F98	307.0, 307.2, 307.3, 307.6, 307.7, 307.9, 312.0, 312.1, 312.3, 312.8, 312.9, 313, 314
Unspecified mental disorder	F99	