RISKS OF ADVERSE HEALTH AND SOCIAL OUTCOMES AMONG CHILDHOOD CANCER SURVIVORS

by

JOYEETA GUHA

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School of Health and Population Sciences
College of Medical and Dental Sciences
University of Birmingham
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ABSTRACT

As a result of improvement in survival after childhood cancer, there are now increasing numbers of long-term survivors of childhood cancer living in the United Kingdom and across Europe. Specific groups of these childhood cancer survivors experience substantial excess risks of adverse health and social outcomes.

Using the population-based British Childhood Cancer Survivor Study (BCCSS) the following areas were investigated: (1) The proportion of survivors on regular long-term hospital follow-up using risk stratification levels of care developed by the BCCSS in partnership with the National Cancer Survivorship Initiative. (2) The risks of adverse health and social outcomes using record-linkage and a self-reported questionnaire to assess which survivors of central nervous system tumours were at excess risk compared to the general population. (3) The risk of hospitalisation due to cerebrovascular conditions among childhood cancer survivors by electronic record linkage with Hospital Episode Statistics. Using the European PanCareSurFup cohort, the excess risks of genitourinary subsequent primary neoplasms were investigated among five-year survivors of childhood cancer.

This thesis quantifies the risks experienced by childhood cancer survivors in four areas and provides an evidence-base for risk stratification by healthcare professionals caring for survivors.

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LIST OF ABBREVIATIONS

AER	absolute excess risk
ALiCCS	Adult Life after Childhood Cancer in Scandinavia Study
ALL	acute lymphoblastic leukaemia
AML	acute myeloid leukaemia
BCCSS	British Childhood Cancer Survivor Study
BMI	body mass index
CAYCAS	Childhood, Adolescent and Young Adult Cancer Survivor Research Program
CCLG	Children's Cancer and Leukaemia Group
CCSS	Childhood Cancer Survivor Study
CI	confidence interval
CML	chronic myeloid leukaemia
CNS	central nervous system
COG	Children's Oncology Group
CTCAE	common terminology criteria for adverse events
DCOG LATER	Dutch Childhood Oncology Registry Late Effects Registry
ECO	European Cancer Observatory
EHR	excess hospitalisation ratio
FCCSS	French Childhood Cancer Survivor Study
FPN	first primary neoplasm
GEE	generalised estimating equation
GHS	General Household Survey
GP	general practitioner
GU	genitourinary
Gy	Gray
HES	Hospital Episode Statistics
HSCIC	Health and Social Centre Information Centre
IARC	International Agency for Research on Cancer
ICCC	International Classification of Childhood Cancer
ICD	International Classification of Diseases
ICD-O-3	International Classification of Diseases for Oncology, third edition
IGHG	International Guideline Harmonisation Group
LREC	local research ethics committee
MREC	multi-centre research ethics committee
NCSI	National Cancer Survivorship Initiative
NHL	Non-Hodgkin lymphoma
NHS	National Health Service
NICER	National Institute for Cancer Epidemiology and Registration
OHLS	Oxford Healthy Life Survey
ONS	Office of National Statistics
OR	odds ratio
PANCARESURFUP	Pancare Childhood and Adolescent Cancer Survivor Care and Follow-up Studies
PNET	primordial neuroectodermal tumour
RER	relative excess risks
RR	relative risk

SCCSS	Swiss Childhood Cancer Survivor Study
SF-36	Short Form-36 Health Status Survey
SHR	standardised hospitalisation ratio
SIR	standardised incidence ratio
SIGN	Scottish Intercollegiate Guidelines Network
SJLIFE	St. Jude Lifetime Cohort Study
SMR	standardised mortality ratio
SPN	subsequent primary neoplasm
WHO	World Health Organisation
WP	work package
UKCCSG	United Kingdom Children's Cancer Study Group
UK	United Kingdom

CHAPTER 1 INTRODUCTION

1.1 DEFINITION OF CHILDHOOD CANCER

Cancer, which can also be termed neoplasm, is the uncontrolled growth of abnormal cells beyond their usual boundaries that can occur in any part of the body. According to the World Health Organisation (WHO) 'childhood cancer' is terminology used for the occurrence of a neoplasm in children before the age of 15 years (1).

1.2 EPIDEMIOLOGY OF CHILDHOOD CANCER

An overview of childhood cancer epidemiology will now be introduced focussing on the incidence and survival of childhood cancer in individuals aged between 0 to 14 years in the United Kingdom (UK), which takes into account the WHO definition (1).

1.2.1 Incidence

Childhood cancer is rare, accounting for less than 1% of all cancers diagnosed (2). In the UK, during the 2009 to 2011 period, there was on average 1,574 new cases of childhood cancer diagnosed per year between the ages of 0 to 14 years inclusive (2). The annual world age-standardised incidence for childhood cancer diagnosed between the ages of 0 and 14 years from 2009 to 2011 in the UK was 144.9 per million children per year (2).

From the late 1960s to the early 2000s, the incidence of childhood cancer has increased 0.9% on average per year in Great Britain (3). An increase in the incidence of childhood cancer over time is a trend that has been observed in other countries in Europe (4). It has been suggested that this temporal increase in childhood cancer incidence could be explained by a number of factors including: earlier detection of cancer through improved diagnostic techniques; changes in levels of environmental carcinogenic risk factors; improvements in ascertainment to cancer registration systems (4-6). However, there is still little known about the causes of childhood cancer, unlike several adult cancers for which there are well established environmental and/or lifestyle risk factors.

Incidence of childhood cancer is highest among individuals aged under five years, with almost half of all childhood cancers (47%) diagnosed in this age category (7). Between 1991 and 2000, the total age-standardised annual incidence rate was highest in children aged less than a year (188 per million) and lowest in children aged between five and nine years (108 per million) respectively (3).

1.2.2 Survival

Overall survival from childhood cancer has increased substantially over time in developed countries. In the UK, the percentage surviving at least five years has increased over the past 30 years from 28% for those diagnosed in the 1960s to 77% for those diagnosed in the 1996 to 2000 period with a further increase to 82% among children diagnosed between 2000 and 2010 (3, 8).

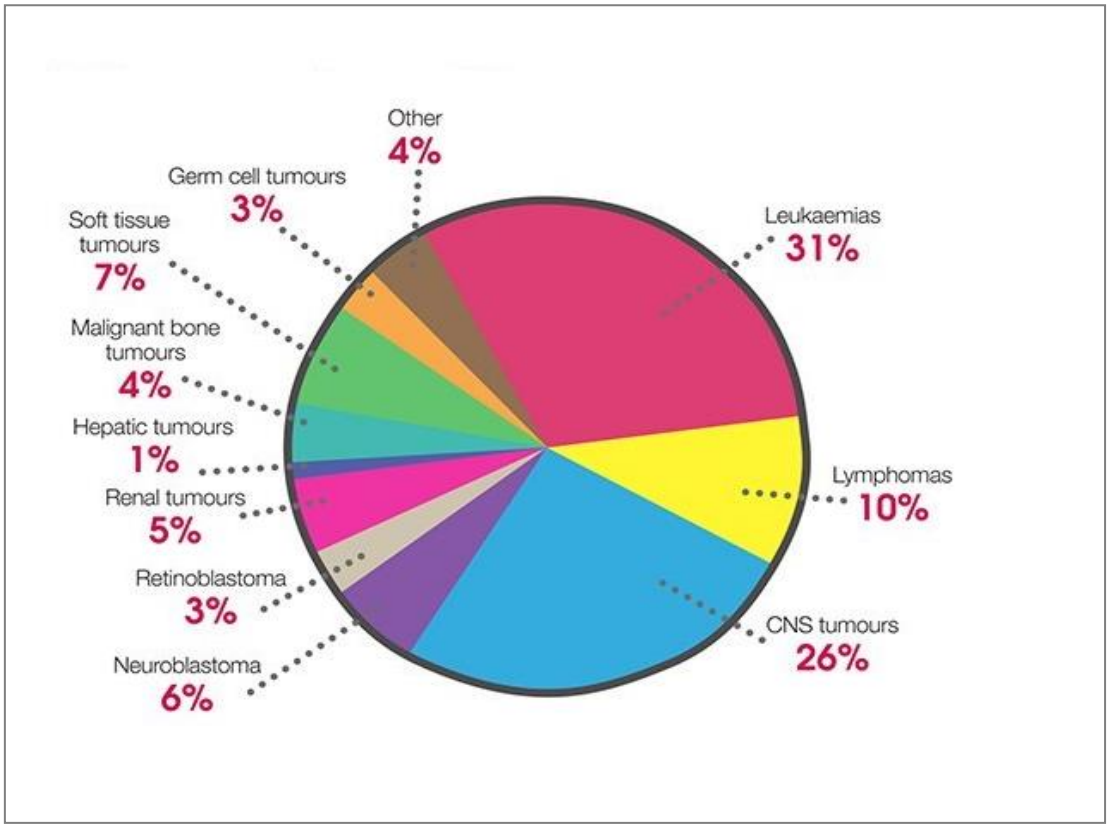
Increases in survival after childhood cancer overall have led to substantial increases in the number of long-term survivors in the general population. For example, in 2012 there were approximately 33,000 survivors living in the UK compared to 26,000 survivors in 2005 (3, 7). Approximately one in 715 young adults is now a long-term survivor of childhood cancer in the UK (9). Improvement in survival after childhood cancer has been attributed to developments in several aspects of modern medicine including: diagnostic techniques (for example, computed tomography and magnetic resonance imaging), paediatric surgery, centralisation of treatment, treatment modalities including chemotherapy and radiotherapy, entry into clinical trials and supportive care (10, 11).

1.3 TYPES OF CHILDHOOD CANCER

Childhood cancers are classified into categories based on the International Classification of Childhood Cancer (ICCC), Third Edition (12) (see Appendix 8.1). The ICCC takes into account the fact that childhood tumours are histologically more diverse than adult cancers,

which are typically coded using the International Classification of Diseases (ICD), a largely site based classification (13). The ICCC relies on tumours being coded using the International Classification of Diseases for Oncology, third edition (ICD-O-3) (14). Therefore the ICCC is based on morphology (type), topography (site) and behaviour code relating to the neoplasm. The diagnostic groups of childhood cancer for all of the analysis in this thesis are thus based on specific groups as defined by the ICCC and those groups not detailed below form a category of 'other' in the analyses. Further descriptions of the diagnostic groups (which can be divided into the broad categories of leukaemia and lymphoma or solid cancers) used throughout the analysis will be presented in the next two sections. Figure 1.1 summarises the main types of childhood cancer diagnosed in the UK.

Figure 1.1 Main types of childhood cancer diagnosed in children aged 0-14 years in the UK between 2001 and 2010 based on data provided by the National Registry of Childhood Tumours (8, 15)



1.3.2 Leukaemia and lymphomas

Leukaemia, a haematological cancer of the blood and bone marrow is the commonest type of childhood cancer, accounting for approximately a third of all childhood cancers (16). Leukaemia can be further classified into acute or chronic. Acute leukaemia, which typically develops and progresses rapidly includes acute lymphoblastic leukaemia (ALL) accounting for 80% of all leukaemia (17) and acute myeloid leukaemia (AML) accounting for 15% of all leukaemia (18). In contrast, chronic leukaemia develops slowly over time and is rarer in children, less than 15 new cases of chronic myeloid leukaemia (CML) are diagnosed annually in the UK (19). Lymphomas arising in the lymphatic system broadly comprise Hodgkin's lymphoma and Non-Hodgkin lymphoma (NHL) which together account for just over 11% of childhood cancers in the UK (17).

1.3.3 Solid cancers

Central nervous system (CNS) tumours of which there are many different subtypes are the second most frequently diagnosed childhood cancer, accounting for over a quarter of all childhood cancers in the UK (16). CNS tumours are usually named after the cell type from which they develop or site of the brain in which they develop, they can be malignant or benign. The most common subtypes of CNS tumours are astrocytomas, which typically account for 40% of all CNS tumours diagnosed. Embryonal tumours, which mainly comprise medulloblastomas or primitive neuroectodermal tumours (PNETs) are the second most common CNS subtypes in childhood and account for 20% of all CNS tumours diagnosed. Ependymomas account for 10% of all CNS tumours diagnosed (20).

Embryonal tumours developing outside the CNS encompass several varieties and only the main types are described here. Neuroblastoma tumours are usually derived from primordial neural crest cells, which are involved in the development of the nervous system. Principally in

childhood they are found in the spine and account for 6% of all childhood cancers diagnosed (15, 21). Retinoblastoma is a malignant tumour of the embryonic neural retina, which can be hereditary (autosomal dominant) or non-hereditary in form and account for 3% of all childhood cancer diagnoses (22, 23). Wilms' tumour, also known as nephroblastoma, originates in the kidney from metanephric blastema cells and can either be unilateral, affecting one kidney or bilateral, affecting both kidneys (24). Wilms' tumour comprise 90% of all renal cancers in childhood and renal cancers collectively account for 5% of all childhood cancer diagnoses in the UK (25).

Soft tissue sarcomas are tumours that arise in connective tissue such as tendons and soft tissue such as muscle and comprise 7% of all childhood cancer diagnoses in the UK (26). Rhabdomyosarcoma is the most prevalent type of soft tissue sarcoma (26). The main types of malignant bone tumours are osteosarcoma and Ewing's sarcoma. Ewing's sarcoma can also originate in the connective tissues (27). Osteosarcoma is more common than Ewing's sarcoma in childhood and together they comprise 4% of childhood cancer diagnoses in the UK (28).

1.4 ESTABLISHED CHILDHOOD CANCER SURVIVOR COHORTS

Various cohorts have been established to investigate childhood cancer survivors since there was a growing need to address survivorship issues, particularly the risks of adverse health and social outcomes, in this population. In Europe, the main cohorts that exist are the Adult Life after Childhood Cancer in Scandinavia (ALiCCS) (29), the British Childhood Cancer Survivor Study (BCCSS) (30), the Dutch Childhood Oncology Group Late Effect Registry (DCOG LATER) (31) and the Swiss Childhood Cancer Survivor Study (SCCSS) (32). In North America, three cohorts exist, the Childhood Cancer Survivor Study (CCSS) (33), the Childhood, Adolescent and Young Adult Cancer Survivor Research Program (CAYCAS) (34) and the St. Jude Lifetime (SJLIFE) Cohort study (35). Other childhood cancer survivor

cohorts exist such as the French Childhood Cancer Survivor Study (FCCSS) (36), Australian childhood cancer survivor cohort based on the New South Wales population (37) and the recently established French Childhood Cancer Survivor Study for Leukaemia (LEA) cohort (38). Two of the cohorts mentioned above have been extended to encompass more recently diagnosed survivors; these include a period of diagnosis which now spans from 1940 to 2006 in the BCCSS and a period of diagnosis from 1971 to 1999 in the CCSS. Table 1.1 summarises some of the key features of the main childhood cancer survivor cohorts that have been established.

European studies investigating survival after childhood cancer such as EUROCARE-5 state that their age range criteria is between 0 and 14 years inclusive as "14 years is usually the cut-off used in studies of childhood cancer" (39). The WHO definition of childhood cancer also takes into account this age range (1). The definition of childhood cancer throughout this thesis follows age at diagnosis of 0-14 years, unless stated otherwise.

Table 1.1 Main characteristics of the established childhood cancer cohorts

Name of cohort	Country/Countries involved	Childhood Cancer types included	Period of FPN diagnosis	Age at FPN diagnosis (years)	Entry criteria (years from diagnosis)	Setting
Adult Life after Childhood Cancer in Scandinavia (ALiCCS)	Denmark Finland Iceland Norway Sweden	Leukaemia, Hodgkin's lymphoma, NHL, CNS tumours, sympathetic nervous system, Retinoblastoma, Renal tumours, Hepatic tumours, malignant bone tumour, soft tissue sarcoma, germ cell and gonadal neoplasm, malignant epithelial neoplasm, other and unspecified neoplasm	1943-2008	<20	≥ 1 year	Population-based
British Childhood Cancer Survivor Study (BCCSS)	England Scotland Wales	Leukaemia, Hodgkin's lymphoma, NHL, CNS tumours, neuroblastoma, Retinoblastoma, Wilm's tumour, bone sarcoma, soft tissue sarcoma, other tumours	1940-1991, recently extended to 2006	<15	≥ 5 years	Population-based
Childhood Cancer Survivor Study (CCSS)	North America	Leukaemia, Hodgkin's lymphoma, NHL, CNS tumours neuroblastoma, Wilm's tumour, soft tissue sarcoma, bone tumour	1970-1986, recently extended to 1999	<21	≥ 5 years	Hospital-based
Childhood, Adolescent and Young Adult Cancer Survivors Research Program (CAYCAS)	Canada - specifically British Columbia	Leukaemia, lymphomas, CNS tumours, sympathetic nervous system, retinoblastoma, renal tumours, hepatic tumours, malignant bone tumours, soft tissue sarcomas, germ cell cancers, carcinomas and other cancers	1970-1995	<25	≥ 5 years	Population-based
Dutch Childhood Oncology Group LAte Effect Registry (DCOG LATER)	Netherlands	Leukaemia, Hodgkin's lymphoma, NHL, CNS tumours, neuroblastoma, Retinoblastoma, Wilm's tumour, bone sarcoma, soft tissue sarcoma, other tumours	1963-2002	<18	≥ 5 years	Hospital-based
Swiss Childhood Cancer Survivor Study (SCCSS)	Switzerland	Leukaemia, lymphomas, CNS tumours, neuroblastoma, retinoblastoma, renal tumours, hepatic tumours, bone tumours, soft tissue sarcomas, germ cell tumours, other malignant epithelial neoplasms, other and unspecified malignant neoplasms, langerhans cell histiocytosis	1976-2010	<21	≥ 5 years	Population-based

FPN: first primary neoplasm

1.5 'LATE EFFECTS' OF CHILDHOOD CANCER AND ITS TREATMENT

Treatments given for childhood cancer involve surgery, chemotherapy or radiotherapy. Each of these forms of therapy may increase the risk of adverse health and social outcomes. Such adverse effects, often termed 'late effects' may occur soon after treatment or many years, up to decades, after treatment has ended (17, 40).

Due to the number of long-term survivors now living many years beyond their original cancer diagnosis, there is a need to investigate the potential long-term health consequences of treatment for cancer. Research has provided evidence that the risk of late effects varies depending on a spectrum of cancer related and demographic factors. It is important that survivors are risk-stratified in relation to the intensity of follow-up care required and that the intensity of follow-up care corresponds closely with the level of risk anticipated (41, 42). Although treatment regimens have changed over recent decades, it is important to estimate the risks of late effects following these evolving therapies to provide risk estimates for existing long-term survivors and to assess potential risks associated with proposed new treatment protocols (43). This is of particular relevance since many cytotoxic drugs and treatment modalities that were used in earlier treatment eras are still used in modern day therapeutic protocols (44, 45).

1.5.1 Overall risk of chronic diseases

In the CCSS, survivors and their siblings completing postal questionnaires resulted in the reported chronic health conditions of 10,397 survivors and 3,094 siblings which were graded using the Common Terminology Criteria for Adverse Events version 3 (CTCAE v3.0), developed by the National Cancer Institute (46). The CTCAE classifies conditions from grade 1 (mild conditions) to grade 5 (fatal, i.e. death) (46). It was found that 62.3% survivors reported having at least one chronic health condition graded 1 to 4, by a mean age of 26.6

years compared to 36.8% of siblings (47). A greater proportion of survivors (27.5%) reported a severe (grade 3) or life-threatening or disabling condition (grade 4) by a mean age of 26.6 years compared to 5.2% of siblings. In relative terms, survivors were three times more likely than their siblings to have a chronic health condition of any grade (47). The cumulative risk of developing at least one chronic condition of any grade by 30 years from diagnosis was 73.4% (47). The CCSS have also investigated the risk of chronic conditions, graded 3, 4 or 5 according to the CTCAE v3.0 (46) in association with attained age (48). By age 50 years, the cumulative incidence of chronic conditions graded at least 3 was 53.6% for survivors compared to 19.8% for siblings (48). Increasing cumulative incidence of particular chronic conditions such as cardiac dysfunction, respiratory impairments and endocrine disease with increasing age of survivors has been reported (49). These findings reinforce the ongoing importance of monitoring survivors many years after their original childhood cancer diagnosis since a large proportion of the survivor population will experience a chronic condition related to their treatment. In a hospital-based Dutch study of 1,362 childhood cancer survivors, the total burden of adverse health outcomes associated with various treatments was investigated (50). Using the CTCAE v3.0 grade of events (46) and the number of events experienced, the survivors were categorised to low (one or more grade 1 event), medium (one or more grade 2 and/or grade 3 event), high (two or more grade 3 events or one grade 4 event) or severe (more grade 3/4 events or grade 5 event) burden (50). This Dutch study found that 75% of survivors had at least one condition of any CTCAE grade by a median attained age of 24.4 years and of those survivors with chronic conditions, 37% of survivors had at least one severe health outcome by the same age (50). Among survivors treated with radiotherapy only, 55% had a high or severe burden of adverse health events by a median attained age of 24.4 years, compared with 25% of survivors treated with surgery alone and 15% of survivors treated with

chemotherapy alone by the same age (50). Among survivors treated with chemotherapy alone (either anthracyclines or alkylating agents or both combined) survivors treated with just anthracyclines had the highest risk (3-fold) of developing a high or severe burden score compared to treatment with other types of chemotherapy (50).

The extent of late effects vary by childhood cancer type, for example, in a study by the CCSS, survivors of a CNS tumour, bone tumour or Hodgkin's disease were at highest risk of developing severe or life-threatening chronic health problems compared to their siblings (47). While in the Dutch hospital-based study which assessed burden of adverse health outcomes, bone tumour survivors were at the highest risk compared to other survivor groups (50). Thus it is important to consider the diagnostic type of the childhood cancer and the treatment given including types of surgery, chemotherapy and radiotherapy received by the survivor. The types of physical late effects survivors may experience have been documented as premature mortality (51-58), subsequent primary neoplasms (59-67) and chronic conditions such as cardiovascular (50, 68-73), endocrine (50, 70, 74-78), gastrointestinal (79, 80), genitourinary (70, 81-90), musculoskeletal (91), respiratory (50, 70, 92-96) and neurological (91, 97-102). The late effects affecting childhood cancer survivors which are the subject of particular focus in this doctoral research will now be detailed.

1.5.2 Premature Mortality

All-cause mortality as well as cause-specific mortality has been investigated in various large scale population-based and hospital-based cohorts; observed mortality rates in all of these cohorts were compared to that expected from age, calendar-period and sex-matched peers in the general population (52-55). Overall mortality among childhood cancer survivors in the BCCSS cohort was 11-times that expected (Standardised Mortality Ratio (SMR)=10.7) (55), in the CCSS cohort, it was 8-times that expected (SMR=8.4) (52) and in the Nordic countries

it was 8-times that expected (SMR=8.3) (54). However, the period of follow-up varies across these studies and as SMRs tend to decline with increased follow-up, one needs to be mindful of this when interpreting these differences. In the CCSS cohort, the cumulative risk of dying by 30 years from diagnosis was 18.1% (52) while in the BCCSS cohort by 50 years from diagnosis, the cumulative risk of dying was 31.4% compared to 6.3% expected from the general population (55). Within the BCCSS, survivors of leukaemia (SMR=21.5) and CNS tumours (SMR=12.9) were found to be at particular high risk of all-cause mortality compared to the general population (55). These findings are consistent with the CCSS who also found survivors of CNS tumours (SMR=12.9) and leukaemia (SMR=10.0) to be at the highest risk of mortality (52). The main causes of the excess number of deaths observed are recurrence or progression of primary cancer in the initial years after childhood diagnosis whereas with increasing time from diagnosis, non-neoplastic causes of death account for most of the excess number of deaths including respiratory, endocrine and cardiac diseases (52, 54, 55).

1.5.3 Subsequent Primary Neoplasms

A subsequent primary neoplasm (SPN) is by definition a neoplasm histologically distinct from the first primary neoplasm (i.e. the childhood cancer) (103). The risk of developing a SPN among childhood cancer survivors has been compared to age, calendar-period and sex-matched underlying general populations (61, 63, 64, 104). In the BCCSS, the risk of survivors developing a SPN was 4-times that expected from the general population (63) while in the CCSS this was 2-times that expected from the relevant general population (104). Survivors in the Nordic countries had an overall risk of developing a SPN 3-times that expected from the relevant general population (64). The cumulative risk of SPNs at 30 years from childhood cancer diagnosis has been reported as 7.9% in the CCSS (60). In a Dutch hospital-based study, the cumulative incidence in five-year childhood cancer survivors at 30 years of follow-

up was 11.1% (59). In the BCCSS, which has longer follow-up compared with the CCSS, the cumulative risk of SPNs at an attained age of 60 years was 13.8% compared to 8.4% expected from the general population (63). The risk of SPNs persist beyond 30 years from initial cancer diagnosis, with particular SPNs such as CNS and bone being more common in the short-term and breast and digestive SPNs being more common in the long-term (63, 64). Some SPNs are typically known to occur after a particular primary childhood cancer diagnosis, such as breast cancer after Hodgkin lymphoma, thyroid cancers after leukaemia or Hodgkin lymphoma and CNS SPNs after a childhood CNS tumour or leukaemia (104) but this is largely explained by treatment for the relevant childhood cancers. As survivors are increasing in numbers and reaching ages where common cancers of mature adulthood typically develop in the general population such as breast, bowel and genitourinary cancers, further investigation is needed (63, 64). The main risk factor for solid cancer is radiation, while for leukaemia it is chemotherapy (60, 61, 105).

1.5.4 Cardiac diseases

Cardiac diseases occurring among childhood cancer survivors include cardiomyopathy/heart failure, ischaemic heart disease, valvular abnormalities, pericardial disease and arrhythmia (49, 68). In the CCSS, survivors were between 5-and 6-times more likely to have an adverse cardiac condition compared to siblings; cardiac conditions included cardiomyopathy/congestive heart failure, myocardial infarction, pericardial disease and valvular abnormalities (68). Of the non-neoplastic causes of mortality observed among survivors, cardiac is the leading cause (51, 54, 55). By 30 years from cancer diagnosis, cardiac deaths accounted for a total of 6.9% of all causes of deaths in the CCSS cohort (51). By 50 years from cancer diagnosis in the BCCSS, the cumulative mortality due to circulatory causes was 3.9% (55). This latter study highlights that survivors remain at elevated risk of

cardiac conditions many years after their original childhood cancer diagnosis. Survivors of Hodgkin's disease are at particular increased risk of cardiac conditions (68, 106). In a clinical cohort, 56.4% of survivors classified as being at risk due to their childhood cancer treatment had cardiac abnormalities, one of the most prevalent chronic conditions among adult survivors of childhood cancer (70). Radiation has been shown to accelerate the atherosclerotic process which increases the risk of ischaemic heart disease (107) while anthracyclines increase the risk of cardiomyopathy and heart failure (108, 109). A hospital-based study in the Netherlands, which had a median follow-up of 17 years found childhood cancer survivors previously treated with anthracyclines in childhood to have a 3-fold risk of an adverse cardiovascular event compared to survivors treated with no chemotherapy (50).

1.5.5 Stroke

In a CCSS study of 14,358 childhood cancer survivors that were followed up for a mean of 23.3 years, the overall relative risk of having a stroke among survivors was 8-times that among siblings (110). Survivors of CNS tumours and leukaemia had the highest risk of stroke among all types of childhood cancer as demonstrated by significantly increased relative risks of 29.0 and 6.4 compared to siblings in the CCSS cohort (111). Survivors of Hodgkin's disease also had elevated risk of stroke with a relative risk of 4.3 compared to siblings (112). Cranial radiation is a risk factor for stroke occurrence among childhood cancer survivors (110) as is treatment with mantle radiation (112). A study by the CCSS has investigated the risk of stroke over time among survivors who were treated with cranial irradiation (110). The cumulative incidence of stroke among CNS tumour survivors treated with cranial irradiation of 50+Gray (Gy) at 30 years after diagnosis was 14.2% compared with 1.3% at 10 years after diagnosis (110).

1.5.6 Respiratory diseases

Respiratory problems investigated among survivors include; lung fibrosis, emphysema, pneumonia, bronchitis, recurrent sinus infections, asthma, hayfever, tonsilitis and shortness of breath (92). In a Dutch hospital-based study of all types of childhood cancer survivors except CNS tumours, 44% (n=85) of survivors had a developed a respiratory functional impairment after a median follow-up of 18 years (95). After five years from diagnosis, of the respiratory conditions investigated in a CCSS study among all types of childhood cancer, the highest estimated incidence rates were observed for bronchitis (13.7 per 1,000 person-years) and for recurrent sinus infections (11.9 per 1,000 person-years) (92). Also in the CCSS, the conditions among survivors associated with the highest relative risks compared with siblings were pneumonia (5-fold) and lung fibrosis (3-fold) (92). Respiratory conditions are one of the most common non-neoplastic causes deaths accounting for almost 3% of all deaths by 30 years from diagnosis in a study by the CCSS (51). Among BCCSS survivors reaching at least 45 years from diagnosis, 7% of all excess deaths were attributable to respiratory causes (55). Of 417 adult survivors of childhood cancer exposed to any of lung radiation, busulfan, carmustine, lomustine, bleomycin or thoracotomy, the prevalence of abnormal respiratory function was 62.5% by a median follow-up of 25.1 years (70). Childhood cancer survivors treated with both chest radiation and chemotherapeutic agents (bleomycin, busulfan, carmustine, cyclophosphamide or lomustine) have shown an increasing cumulative incidence over time of lung fibrosis, pleurisy, chronic cough and exercise exacerbated shortness of breath (92). Survivors at particular increased risk of respiratory complications include CNS tumour survivors (96) and leukaemia (113).

1.5.7 Endocrine

Endocrine disorders are diverse and can be a driving factor for other health conditions to develop such as cardiovascular disease (114). Treatment-related endocrine disorders can have both a physical and psychological impact on a survivor, which can affect the quality of life a survivor leads (114). In a SJLIFE study, the prevalence of endocrine problems was 62.5% after a median follow-up of 25.1 years among adult survivors treated for childhood cancer with any of following: radiation to the hypothalamic-pituitary axis, neck, male or female reproductive organs or alkylating agents (70). Medical assessment of endocrine disorders that developed among childhood cancer survivors in a Dutch hospital-based study revealed 5.3% as severe, life-threatening or disabling or fatal by a median attained age of 24.4 years (50). Survivors at the greatest excess risk of hospital contact for endocrine disorders in an ALiCCS study included leukaemia (standardised hospitalisation rate ratio (SHRR)=7.3, 95%CI:6.7-7.9), CNS tumours (SHRR=6.6, 95%CI:6.2-7.0) and Hodgkin's lymphoma (SHRR=6.2, 95%CI:5.6-7.0) (75). The cumulative risk of endocrine disorders for survivors aged 60 years was 42% in the ALiCCS study (75). CNS tumour survivors (76), Hodgkin's disease survivors (115), neuroblastoma survivors (91) and leukaemia survivors (116) have all been reported to be at high risk of endocrine problems in various studies by the CCSS. Endocrine dysfunction can occur due to damage of the hypothalamic-pituitary axis as a result of either proximity of neoplastic development close to the axis or from cancer treatments close to the axis such as surgery or cranial radiotherapy (74). The hypothalamic-pituitary axis is critically important for the regulation of hormone production and impairment to this axis can cause hormonal imbalance and neuroendocrine abnormalities (114). A study from the Netherlands demonstrated survivors who received radiation directly exposing the head and neck to be at 8-times the risk of developing an endocrine adverse event compared to survivors who had not been treated with radiotherapy (50). Radiation has been documented to elevate the risk of

hypothyroidism, hyperthyroidism and thyroid cancers among survivors of Hodgkin's disease and survivors of ALL (77, 115, 117). Total body irradiation and radioactive iodine are other modalities of treatment which are associated with an increased risk of endocrine conditions (50). Treatment with alkylating agents can cause gonadal problems such as testicular dysfunction (118), acute ovarian failure (119) or premature menopause (120). Adult survivors treated with radiation and/or alkylating agents for childhood cancer experienced a prevalence of 56.4% for disorders of the hypothalamic-pituitary axis, 13.8% for hypothyroidism, 66.4% for testicular dysfunction and 11.8% for primary ovarian failure by a median follow-up of 25.1 years (70).

1.5.8 Nervous system disorders

Nervous system disorders include a spectrum of neurological and neurocognitive deficits (70). Neurological problems can include neurosensory deficits, seizures or convulsions or motor dysfunction (99). Neurocognitive problems can include deficits in executive function, memory, processing speed, sustained attention, visual motor integration, fine motor dexterity, diminished Intelligence Quotient or behavioural change (121). Nervous system disorders were one of the most prevalent conditions identified among adult survivors of childhood cancer investigated as part of the St. Jude Lifetime cohort with a prevalence greater than 20% for each neurocognitive or neurosensory condition by a median follow-up of 25.1 years (70). Risk factors for neurological and neurocognitive problems include previous treatment with cranial irradiation, total body irradiation, and a whole host of chemotherapeutic drugs such as platinum agents (cisplatin and carboplatin), antimetabolites (methotrexate) and alkylating agents (busulfan) (70, 98, 99). Childhood cancer survivors at particular increased risk of neurological and neurocognitive disorders include CNS tumour survivors (99, 100), leukaemia survivors (98) and neuroblastoma survivors (91).

1.5.9 Hospitalisations

It is important to quantify the extent to which increased morbidity observed among survivors translates into excess use of healthcare and in particular hospital facilities. This is likely to be helpful for healthcare planning purposes as well as identifying groups of survivors who may need closer clinical monitoring (122). Both the CCSS and BCCSS have investigated the use of healthcare among survivors by using self-reported questionnaires (122, 123). In a study by the CCSS, the overall rate of hospitalisation among survivors was 1.6-times that expected from the general population (122). In the BCCSS, survivors were twice as likely to have been hospitalised as an inpatient with an overnight stay at least once in the last year compared to that expected from the general population (123). The CCSS found survivors of Hodgkin's disease had twice the rate of hospitalisation compared to that expected from the general population (Standardised Incidence Ratio (SIR)=2.2, 95%CI: 2.1-2.3) (122) while the BCCSS reported that CNS tumour survivors (Odds Ratio (OR) =2.4, 95%CI:2.0-2.8) and survivors of bone sarcoma (OR=2.3, 95% CI:1.6-3.2) were twice as likely to be hospitalised as an inpatient compared to the general population (123). Neuroblastoma survivors were also associated with higher risks of hospitalisations than expected from the general population in both studies (122, 123). In a Canadian study, CNS tumour survivors demonstrated the highest excess risk of developing multiple late conditions, graded 3 or above according to the CTCAE v3.0 (46) that lead to hospitalisation (124).

1.5.10 Psychosocial outcomes

Late effects are not solely restricted to those that impact of health but also include those that impact social aspects of life. Psychosocial outcomes can encompass education, employment, marriage and health related quality of life (125). Such outcomes are important to an individual's life course. Social outcomes of relevance to this thesis are summarised next.

Various studies have investigated educational attainment among childhood cancer survivors compared to underlying general populations, siblings or comparators selected from general practitioner registry lists (126-129). There is concordance from the UK, North America, Switzerland and Denmark that CNS tumour survivors had the lowest levels of educational attainment compared to the relevant comparator populations (126-129). Survivors of leukaemia, NHL and neuroblastoma have also shown deficits in their educational attainment compared to sibling controls (129). A population-based Canadian study reported that parents of survivors of CNS tumours, leukaemia and neuroblastoma were more likely to report poorer education outcomes such as failing or repeating a school grade compared to parents of controls who did not have cancer (130). In terms of cancer therapy, survivors treated with cranial irradiation have shown greater deficits in their educational attainment across a spectrum of education levels compared to those survivors who did not receive cranial irradiation (128). Cranial irradiation doses of $\leq$25Gy was the strongest explanatory factor for lower educational levels among survivors in a study from the Netherlands (131). A possible explanation given for this finding is that almost a third of survivors that received this dose of cranial irradiation were aged 6 years or less and literature has reported younger age at treatment as a risk factor for cognitive impairment (131). Furthermore, survivors who received either cranial irradiation and/or intrathecal methotrexate were significantly more likely to use special education services compared to those survivors who had not received either of these treatment modalities (129).

Lifestyle factors such as smoking and alcohol consumption are risk factors for various health conditions and illnesses such as cancers, cardiovascular disease, respiratory problems and liver disease (132, 133). Thus these behaviours should be discouraged in survivors who may

already be at increased risk of these chronic health conditions as a result of their original childhood cancer diagnosis and/or treatment.

In the BCCSS, childhood cancer survivors of all types had half the odds (OR=0.52, 99%CI:0.46-0.60) of being a current drinker compared to that expected from the general population (134). However, in the CCSS, childhood cancer survivors were slightly more likely to be current drinkers (OR=1.1, 95%CI:1.0-1.2) compared to national peers (135). CNS tumour survivors and leukaemia survivors were the least likely to be current drinkers compared with the general population while NHL survivors and bone sarcoma were closest to the general population in their odds of being a current drinker in the BCCSS (134). All childhood cancer survivors were less likely than the general population to consume alcohol over recommendations (OR=0.65, 99%CI:0.58-0.73) or harmful amounts of alcohol (OR=0.40, 99%CI:0.32-0.49) compared to the general population in the BCCSS (134). Childhood cancer survivors in the CCSS were less likely to be risky drinkers (OR=0.9, 95%CI:0.8-1.0) or heavy drinkers (OR=0.8, 95%CI:0.7-1.0) compared to national peers (135). A Canadian study also reported childhood cancer survivors being less likely to be binge drinkers (OR=0.66, 95%CI:0.55-0.78) compared to population controls selected from provincial health insurance registries or random digit dialling (136). Survivors of Hodgkin's lymphoma, Wilms' tumour, NHL and soft tissue sarcoma were comparable to the general population in consuming alcohol above recommendations (134). Treatment with cranial irradiation (OR=0.46, 99%CI:0.39-0.55) showed even greater deficits than those who had not received such treatment (OR=0.71, 99%CI:0.61-0.83) in being a current drinker (134). Risk factors reported for survivors being a heavy drinker included being male (135-137) and low educational attainment (135, 136). A study by the SCCSS however found higher education achievement to be associated with frequent alcohol consumption among survivors (137).

Drinking initiation at a young age has also been reported as being a risk factor for heavy drinking among childhood cancer survivors (135).

In the BCCSS, survivors of all types of childhood cancer had half the odds of being a current regular smoker (OR=0.51, 99%CI:0.46-0.57) than expected from the general population (138). This finding is consistent with a Canadian study which reported survivors being less likely to be current smokers (OR=0.65, 95%CI:0.54-0.77) than population controls (136). Survivors closest to the general population in their odds of being a current regular smoker were non-heritable retinoblastoma survivors, Hodgkin lymphoma survivors and soft tissue sarcoma survivors (138). Some risk factors for smoking initiation among survivors have been identified as low income and low educational attainment (136, 139).

Even though it is somewhat reassuring that survivors are not displaying worse health behaviours compared to underlying general populations, there are still survivors who are smoking regularly, consuming alcohol over recommended limits and consuming harmful quantities of alcohol, which is of concern given the types of treatment some of these survivors may have received. In a Canadian study, no difference was reported in being a current smoker among childhood survivors who had been treated with cardiac/pulmonary toxic therapy compared to those who had not received this therapy (136). Thus health promotion interventions and initiatives regarding smoking and alcohol consumption need to be an ongoing consideration for survivors of childhood cancer.

The ability to form relationships is an important transition from adolescence into adulthood (140). Several studies investigating marriage reveal survivors being less likely to marry compared to their respective comparators, in particular survivors that were diagnosed with CNS tumours or treated with cranial irradiation (141-144). Male survivors in particular are less likely to marry when compared to underlying general populations (141, 144).

Investigation of the impact of treatment for childhood cancer on self-assessed health related quality of life is important as it may reveal problems not apparent from the investigation of adverse health and social outcomes alone.

One measure that can be used to determine health related quality of life among childhood cancer survivors is the Medical Outcomes Short Form Survey (SF-36) (145-149). The SF-36 consists of 36 questions, which are summarised into eight scales and two summary components; physical and mental (150). In studies conducted in the UK, North America and Switzerland, childhood cancer survivors scored lower on the physical component summary compared to population norms and siblings (145, 146, 149). In terms of the eight scales, lower scores were reported for physical functioning, role limitation physical and general health among CNS tumour survivors, soft tissue sarcoma, lymphoma and bone tumour survivors compared to siblings (145). Overall childhood cancer survivors compared to siblings did not differ in relation to the scale of bodily pain (149) while closer inspection of survivor groups in another study revealed bone tumour survivors reporting significantly worse bodily pain compared to siblings (145). With respect to the mental component summary, survivors either scored higher than siblings as shown by the SCCSS (149) or showed no difference compared to siblings as shown by the CCSS (145). Findings from the BCCSS also showed that there was no significant difference in the mental component summary scores between all childhood cancer survivors and the comparative normal population (146). However several studies found that upon inspection of survivor groups, CNS tumour survivors and bone tumour survivors scored lower than population norms in relation to the mental component summary scores (146). Treatment risk factors for scoring low on the physical component summary of the SF-36 include surgery, cranial or spinal irradiation, bone marrow transplant and

chemotherapy (145, 149). Other factors associated with poor health related quality of life include being female, older age and lower educational attainment (145).

There are a whole host of late effects that can affect survivors. In providing survivorship care, it is critically important that healthcare providers take into account both medical and psychosocial late effects and the impact they have on general health, mental health and function (151).

1.6 LONG-TERM CLINICAL FOLLOW-UP CARE OF CHILDHOOD CANCER SURVIVORS

The extent of long-term clinical follow-up care survivors receive after their cancer treatment is complete should be evidence-based on their risks of adverse health outcomes. Until relatively recently many clinicians considered that clinical follow-up of childhood cancer survivors should be life-long in order to detect any potential late effects as well as providing advice and counselling to survivors (152, 153). Furthermore, most of the long-term clinical follow-up care of childhood cancer survivors in the UK is provided by medical consultants in hospitals (154). However as the number of long-term survivors continues to increase, it will not be feasible to sustain the practice of every childhood cancer survivor in the UK being on hospital follow-up (155). A survey of clinicians in the UK's Children Cancer Study Group (UKCCSG) centres revealed that long-term clinical follow-up in the UK was not evidence-based but dependent on the treatment centre and clinician involved (156).

The National Cancer Survivorship Initiative (NCSI) which was developed as a partnership between the Department of Health, National Health Service (NHS) Improvement and Macmillan Cancer UK aimed at improving the care and support of people living with and beyond cancer (157). In their Children and Young People Workstream, the NCSI investigated which survivors were at low, medium or high risk of late effects (known as risk stratification) as a consequence of their cancer and its treatment. Since survivors are known to have varying

risks of late effects, the proposal was to develop risk stratified levels of clinical follow-up care. The NCSI has also explored alternative models of follow-up care which could correspond to the risk survivors experience; those at highest risk would still receive medical consultant care in a hospital. Different models of follow-up care have been suggested that include postal follow-up or telephone follow-up (153, 158), supported self-management care (155), primary care-led follow-up (159), nurse-led follow-up (153, 159, 160) and shared care follow-up between primary and secondary or tertiary care (159, 161). Since some survivors have showed preference in receiving hospital follow-up care (162, 163), any proposed changes in long-term clinical follow-up care needs to involve consultation with this population so their requirements, concerns and any perceived barriers to alternative models of follow-up may be addressed. The future of long-term clinical follow-up care of childhood cancer survivors in the UK ought to be evidence-based as this has been previously lacking.

1.7 LONG-TERM CLINICAL FOLLOW-UP GUIDELINES

It is important that the extent and nature of clinical follow-up offered to survivors should relate to their long-term risk of adverse outcomes. Ideally guidelines should be evidence-based and updated regularly as further evidence is produced. These evidence-based clinical guidelines aim to inform clinicians involved in the long-term clinical follow-up of childhood cancer survivors irrespective of whether these clinicians are practising in primary, secondary or tertiary care.

Two clinical guidelines have been developed in the UK, these are the Children's Cancer and Leukaemia Group (CCLG) (164) and Scottish Intercollegiate Guidance Network (SIGN) guidelines (17). From the United States, there are the Children's Oncology Group (COG) guidelines (121). These three clinical guidelines are updated regularly taking account of best evidence through publications and websites. Such updating is reflected in that all three current

guidelines were preceded by earlier published guidelines (165-167). Clinical guidelines in the Netherlands have also been developed, but are available in Dutch only (168).

As the evidence base relating to the risks of late effects is expanding and various research groups across the world are conducting research among childhood cancer survivors, more independent guidelines are being published. Since these guidelines do not always demonstrate consistency in their recommendations whether it be whom to screen, when to screen or other tests that may be appropriate, ambiguity arises as to which guideline is best to follow (169). Thus an International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) was founded in 2010 with the goal of developing guidelines through collaborative efforts in order for survivors to a) receive the best care possible to reduce the consequences of late effects and b) improve their quality of life (170). It is anticipated that there will be less duplication of work; resources will be used more efficiently and there will be pooling of expert knowledge. The first two guidelines from the IGHG have been published, which proves that the goal of an integrated, collaborative strategy is working (171, 172). There are other guidelines in the process of being formulated that include the topics of thyroid cancer and male and female gonadal dysfunction (170).

There will be an ongoing programme of updating such guidelines as the evidence base increases.

1.7.1 PanCare and PanCare Childhood and Adolescent Cancer Survivor Care and Follow-up Studies (PanCareSurFup)

PanCare is a European Network for the Care of Survivors after Childhood and Adolescent Cancer that was founded in 2008 (173). Thirteen countries across Europe are involved in this network. Six questionnaire surveys were conducted to better understand the current landscape of childhood and adolescent cancer research within Europe. Surveys included assessing the

follow-up care after childhood cancer and assessing the process of establishing guidelines for long-term follow-up care for survivors of childhood and adolescent cancer in Europe (174). The findings from these surveys provided an evidence-base for countries across Europe to work collaboratively towards the common goal of providing optimal care for all childhood and adolescent cancer survivors. One project that was set up to meet the aims of PanCare was Pancare Childhood and Adolescent Cancer Survivor Care and Follow-up Studies (PanCareSurFup) which included evaluating long-term risks of childhood cancer treatment, developing evidence-based guidelines and providing education and dissemination of information to survivors and clinicians.

PanCareSurFup was established in 2011, a Seventh Framework Programme funded by the European Union (Grant Agreement Number: 257505). PanCareSurFup is arranged into eight Work Packages (WP) and each WP assumes responsibility for a part of the project. There are WPs which aim to provide risk estimates through cohort and case-control studies with regards to cardiac disease (WP3), SPNs (WP4) and late mortality (WP5) with the intention of improving existing clinical guidelines.

1.8 RATIONALE OF PHD RESEARCH

There is growing evidence to inform childhood cancer survivorship guidelines and it is imperative that these guidelines are evidence-based. The BCCSS is one of the few childhood cancer survivor cohorts that is population-based in nature and thus able to provide unbiased, reliable risk estimates of adverse health and social outcomes. As the date of diagnosis of childhood cancer dates as far back as 1940 in the BCCSS, the length of follow-up is substantial compared to other childhood cohorts such as the CCSS (33), SCCSS (32) and DCOG LaTER study (31) which enables investigation of late effects up to 50 years after initial cancer diagnosis (see Table 1.1 for a comparison of these cohorts). Childhood cancer

survivors are a heterogeneous population in terms of the risk of late effects they will encounter thus it is essential to provide an evidence base to guide which survivors need closer monitoring with regards to each specific late effect. The focus of research presented in this thesis should lead to improvements in existing clinical follow-up guidelines by providing new quantitative evidence of risks of adverse health outcomes and variation in such risks with factors relating to the cancer, its treatment and demographic characteristics.

1.9 OBJECTIVES

The objectives of this thesis are:

1. Investigate which survivors in the BCCSS are on long-term hospital follow-up in relation to the proposed levels of risk stratification developed by the BCCSS in collaboration with the NCSI (157).

2. Explore which subgroups of survivors of CNS tumours within the BCCSS are at risk of adverse health and social outcomes using record-linkage and questionnaire data and compare excess risks to the general population.

3. Investigate which groups of survivors within the extended BCCSS cohort are at excess risk of hospitalisations for cerebrovascular events in England using record linkage with the national Hospital Episode Statistics (HES) database.

4. Quantify the excess risk of genitourinary subsequent primary neoplasms in the PanCareSurFup European cohort of survivors of childhood cancer.

1.10 THESIS OUTLINE

Chapter Two concerns the assessment of survivors that are on regular long-term hospital follow-up in the UK and the willingness of General Practitioners (GPs) to provide advice to survivors in relation to personal medical questions and late effects. Chapter Three reports on the risk of adverse health and social outcomes among survivors initially diagnosed with a CNS tumour within the BCCSS compared to that expected from the general UK population.

Chapter Four concerns the risk of cerebrovascular hospitalisations among BCCSS survivors using record linkage with HES. Chapter Five describes the risk of genitourinary subsequent primary neoplasms among childhood cancer survivors using the PanCareSurFup cohort. Finally, Chapter Six provides a discussion of the main findings of the research conducted for this thesis with implications for current long-term clinical follow-up guidelines and recommendations for future research.

For Chapters Two and Three, the data had already been collected and I was not involved in study questionnaire send outs, data coding or data entry. The dataset was essentially prepared and I carried out some data cleaning before conducting analysis. For Chapter Four, the BCCSS cohort was linked externally with the Hospital Episode Statistics Data by Northgate Solutions. However extensive data cleaning was conducted by myself and other members of the research team independently before analysis was initiated. For Chapter Five, I was involved in extensive cleaning of the data once the dataset had been transferred from the University of Mainz in Germany, assisted with ICD-O conversions and ICD conversions through the IARC programme and liaised with data providers in terms of queries that arose from ICD-O conversions alongside other members of the research team in Birmingham.

CHAPTER 2 NATIONWIDE LONG-TERM CLINICAL FOLLOW-UP OF ADULT SURVIVORS OF CHILDHOOD CANCER: EVIDENCE OF GROUPS WHO NEED THEIR NHS CARE PLAN REVIEWED

2.1 ABSTRACT

Background: Restructuring of clinical long-term follow-up within the National Health Service (NHS) in England has been proposed as part of the National Cancer Survivorship Initiative (NCSI), a key element of the Improving Outcomes: A Strategy for Cancer of the Department of Health for England. Objectives were to investigate the proportion of adult survivors of childhood cancer throughout Britain who are regularly followed-up in a hospital clinic and to explore variation in this proportion with age of survivor and the survivor's estimated long-term risk of serious adverse health outcomes as defined by the National Cancer Survivorship Initiative Level of care: LEVEL 1(low risk); LEVEL 2 (intermediate risk); LEVEL 3 (high risk).

Methods: The British Childhood Cancer Survivor Study (BCCSS) is a population-based cohort of 17,980 five-year survivors of childhood cancer diagnosed <15 years between 1940-1991 in Great Britain. 14,836 of 17,980 survivors were eligible to receive a postal questionnaire. By means of a postal survey, 14,223 General Practitioners (GPs) were contacted for consent to approach survivors; 12,978 GPs returned a completed consent form with information relating to the survivor's clinical follow-up status. Main outcome measures were percentages of childhood cancer survivors on regular hospital follow-up, and GPs willing to provide advice to survivors, in relation to demographic, cancer and treatment factors.

Results: Among LEVEL 3 survivors of non-leukaemic cancer only 31% were on regular hospital follow-up, despite the NCSI recommendation for all LEVEL 3 survivors to be on regular hospital multi-disciplinary team review, furthermore this percentage declined from 57% to 16% among survivors aged under 20 years to survivors aged at least 50 years, respectively. Among LEVEL 1 survivors of non-leukaemia cancers 12% were on regular hospital follow-up, whilst the NCSI recommendation for all LEVEL 1 survivors is self-care

with support. GPs returns indicated that 74% (9595/12978) were willing to discuss survivorship issues with survivors.

Conclusion: Consideration needs to be given to the potential recall of both NCSI LEVEL 3 survivors who are not on regular hospital follow-up for possible establishment of such follow-up, and NCSI LEVEL 1 survivors who are on such follow-up for possible discharge to self-care with support.

2.2 INTRODUCTION

Comprehensive reorganisation of the clinical follow-up of survivors of cancer within the National Health Service (NHS) has been proposed by the National Cancer Survivorship Initiative (NCSI), an important element of the Improving Outcomes: A Strategy for Cancer, produced by the Department of Health for England, and of which this research was part. Before the NCSI, our survey of Children's Cancer and Leukaemia Group Centres, revealed considerable variation in clinical long-term follow-up practices between Centres (156). The NCSI proposes that the level of clinical follow-up care offered to each survivor should be stratified and correspond to their anticipated level of risk of serious adverse health outcomes (154, 155). Such risk stratification is based principally on type of cancer and treatment received and ranges from LEVEL 1 (self-care with support and open access to the healthcare system, with or without reference to a General Practitioner (GP)) to LEVEL 3 (regular hospital multi-disciplinary team review). Intermediate is LEVEL 2 (shared care with planned reviews potentially involving medical and/or nursing specialists in hospitals, and/or GPs with either face-to-face or telephone contact).

As part of the BCCSS, GPs throughout Britain were contacted who were responsible for the care of most adult survivors of childhood cancer in Britain. The GPs were asked whether their patient was still on regular long-term hospital follow-up in relation to their childhood cancer and whether they would be prepared to discuss personal medical questions which might arise from the survivor completing the BCCSS questionnaire (see Appendix 8.2).

Our novel contribution here relates to our investigation of the clinical follow-up status of the entire population-based group of adult survivors of childhood cancer throughout Britain. We explore the percentage of survivors on regular long-term hospital follow-up in relation to their childhood cancer, how this varies with age of the survivor and other characteristics; also

whether there is evidence of individuals not on hospital follow-up who may be at increased risk of serious adverse health outcomes.

2.2.1 Objectives

Our objectives were: (1) Quantify the percentage of the national population of adult survivors of childhood cancer who were regularly seen in a hospital clinic in relation to their childhood cancer prior to the NCSI and explore factors related to variations in this percentage. (2) After assigning each survivor to the appropriate LEVEL 1, 2 or 3 of clinical follow-up care proposed by the NCSI, using type of childhood cancer and treatment information available to the BCCSS, explore the extent of regular long-term hospital follow-up experienced by survivors with increasing attained ages. In particular determine the extent to which LEVEL 3 survivors were not on regular long-term hospital follow-up and the extent to which LEVEL 1 survivors were on such hospital follow-up. (3) Quantify the percentage of GPs who were willing to discuss personal medical questions with survivors relating to survivorship and late consequences of treatment, generated by the BCCSS questionnaire, and investigate factors related to variations in this percentage.

2.3 METHODS

2.3.1 British Childhood Cancer Survivor Study cohort

The British Childhood Cancer Survivor Study (BCCSS) was based on a cohort of 17,980 individuals who were diagnosed with cancer when aged 0-14 years inclusive, between 1940 and 1991, in Britain, and who survived at least five years from diagnosis. The BCCSS cohort of survivors was identified using the population-based National Registry of Childhood Tumours. The BCCSS objectives, study population and methodology have been described in detail previously (30). Ethical approval for the study was obtained from the Multi-Centre

Research Ethics Committee (MREC) in the West Midlands and every Local Research Ethics Committee (LREC) in Britain.

2.3.2 Regular long-term hospital follow-up and associated outcome measures

The BCCSS postal questionnaire was designed to ascertain adverse health and social outcomes occurring among survivors. A total of 14,836 adult survivors were eligible to receive a postal questionnaire, in that they were aged at least 16 years and alive. The GP of each survivor was identified through record linkage with the National Health Service Central Registers. GPs were contacted initially in this study with a consent form as they were considered the key 'gatekeepers' to the survivors. In addition to seeking consent to contact their patient, the GPs were also asked: "*Is your patient still on regular long-term hospital follow-up in relation to their childhood neoplastic disease?;* YES or NO"; "*Would you be prepared to discuss with the patient personal medical questions which might arise as a result of completing the questionnaire?*; YES or NO". From the 14,223 GPs for whom contact details were obtained, 12,978 (91% response rate) completed and returned the consent forms with these additional questions completed.

2.3.3 Statistical methods

Multivariable logistic regression was used to examine potential explanatory factors associated with two outcomes: whether survivors were on such regular long-term hospital follow-up; whether the GP was willing to discuss such medical questions with the survivor. Explanatory factors investigated in relation to each outcome were sex; attained age; childhood cancer type; age at childhood cancer diagnosis; whether treatment involved surgery, chemotherapy or radiotherapy with the latter being coded according to anatomical site of direct exposure; area of residence within Great Britain. Decade of treatment and period of follow-up were not included in the multivariable models due to strong collinearity with attained age. Within each

model and for each specific factor, likelihood ratio tests were used to assess the statistical significance. The strength of association was quantified using the Odds Ratio (OR). Statistical significance was taken at the 5% level (two sided tests). Analyses were carried out using Stata statistical software (version 12.0; Stata Corp., College Station, TX).

For the outcome of whether survivors were on regular long-term hospital follow-up, the effect of an additional potential explanatory factor, classification of each childhood cancer survivor according to their NCSI level of clinical follow-up (155), was investigated. The NCSI levels of follow-up for acute lymphoblastic leukaemia (ALL) survivors were defined as follows: LEVEL 1- no radiotherapy; LEVEL 2- radiotherapy under 24 Gray (Gy); LEVEL 3 - radiotherapy of at least 24 Gy or relapsed or bone marrow transplant (BMT) as part of their initial treatment. For survivors of childhood cancers other than leukaemia, the NSCI Levels of follow-up were defined on the basis of childhood cancer type and the treatment received ─ see Figure 2.1. For both ALL survivors and survivors of childhood cancers other than leukaemia, histograms were created to investigate the percentage of survivors on regular long-term hospital follow-up across different specific attained ages, for survivors allocated to each of the NCSI Levels of clinical care 1, 2 and 3.

2.4 RESULTS

2.4.1 Factors related to the percentage of survivors on regular long-term hospital follow-up

Overall, 36% (4,707 of 12,978 survivors for whom consent forms were returned), were on regular long-term hospital follow-up (Table 2.1). Table 2.1 reveals that age is the strongest explanatory factor with the percentage of survivors on such follow-up declining from 62% among those aged under 20 years, to 9% among those aged at least 50 years.

The percentage of survivors on regular long-term hospital follow-up varied substantially by type of childhood cancer ($P<0.001$). Compared to Wilms' tumour survivors, a significantly

higher odds ratio (OR) of being on follow-up was observed for survivors of leukaemia (OR=1.21, 95% confidence interval (CI):1.04-1.41) and Hodgkin's lymphoma (OR=1.28, 95%CI:1.04-1.57), and significantly lower ORs were observed for neuroblastoma (OR=0.69, 95%CI:0.55-0.88), non-heritable retinoblastoma (OR=0.23, 95%CI:0.17-0.31) and other neoplasms (OR=0.69, 95%CI:0.56-0.84).

The OR of survivors being on such follow-up increased with age of diagnosis ($P_{trend}<0.001$) from 1.00 for the referent group of survivors aged 0-4 years at diagnosis to 1.49 (95%CI:1.32-1.68) for survivors aged 10-14 years at diagnosis in a linear fashion ($P_{non\text{-}linearity}=0.42$).

Survivors treated with chemotherapy were more likely to be on such follow-up than those survivors who had not been treated with chemotherapy. Compared to survivors not treated with any radiotherapy, survivors treated with cranial irradiation were more likely to be on such follow-up (OR=1.76, 95%CI:1.54-2.03) and to a lesser extent, survivors treated with radiotherapy which excluded the head and abdomen were more likely to be on follow-up (OR=1.45, 95%CI:1.23-1.71).

In terms of geographical location, survivors residing in the North West (OR=1.86, 95%CI:1.58-2.21), West Midlands (OR=1.37, 95%CI:1.15-1.64), Scotland (OR=1.32, 95%CI:1.10-1.58) and Yorkshire and Humber (OR=1.19, 95%CI:0.99-1.42), were more likely to be on such follow-up than survivors in London.

2.4.2 Factors related to general practitioners willingness to provide medical advice to survivors

Overall, 74%, 9,595 of 12,978 GPs returning consent forms were willing to provide medical advice to survivors in relation to their childhood cancer. GPs were more willing to provide medical advice to female survivors (OR=1.20, 95%CI:1.10-1.30) than male survivors.

Although there was statistical evidence of variation (P=0.036) across type of cancer, inspection of specific values of odds ratios revealed that the effect was not strong.

GPs were more willing to provide advice (P<0.001) to survivors residing in the North East (OR=1.50, 95%CI:1.19-1.88), Scotland (OR=1.40, 95%CI:1.17-1.69), South East (OR=1.37, 95%CI:1.16-1.61), South West (OR=1.29, 95%CI:1.08-1.54), Wales (OR=1.26, 95%CI:1.02-1.57) and North West (OR=1.19, 95%CI:1.00-1.40), than to survivors residing in London.

2.4.3 Extent of regular long-term hospital follow-up among survivors by age for each National Cancer Survivorship Initiative Level of clinical care

In Figures 2.2a and 2.2b we provide the extent of regular long-term hospital follow-up among survivors in relation to the NCSI Levels of clinical follow-up care and attained age of the survivor. Figures 2.2a and 2.2b relate to survivors of all childhood cancers except leukaemia and survivors of ALL, respectively. There are two clear patterns apparent from Figure 2.2a: within age groups, the percentage on hospital follow-up increases with increasing NCSI Level of clinical follow-up care; between age groups, there is a substantial decline in the percentage of survivors on hospital follow-up with increasing age for each NCSI Level of clinical follow-up care. From Figure 2.2b there is also evidence of a substantial decline in the percentage on hospital follow-up with increasing age for each NCSI Level of clinical follow-up care.

2.4.4 NCSI LEVEL 1 survivors

Overall, 118 (12%) of the 1,026 survivors of non-leukaemic childhood cancers assigned to NCSI LEVEL 1 were still on regular hospital follow-up even though the type of follow-up associated with this Level is self-care with support and open access to the healthcare system, but the survivors were widely spread across a broad spectrum of types of childhood cancer. This percentage of survivors on follow-up declined with age from 22% to 3% among survivors aged under 20 years to those survivors aged at least 50 years, respectively. The

corresponding overall figure for survivors of ALL was 103 (66%) of 156, but 127 (81%) of the 156 were still aged under 20 years.

2.4.5 NCSI LEVEL 2 survivors

Overall, 601 (24%) of the 2,469 survivors of non-leukaemic childhood cancers assigned to NCSI LEVEL 2 were still on regular hospital follow-up. The percentage of survivors on follow-up declined with age from 49% to 9% among survivors aged under 20 years, to those aged at least 50 years, respectively. Overall among survivors of ALL, 472 (48%) of the 974 were on hospital follow-up and this percentage of ALL survivors on follow-up declined with age from 64% among survivors aged under 20 years to 37% among survivors aged at least 30 years.

2.4.6 NCSI LEVEL 3 survivors

Of the non-leukaemic childhood cancer survivors, only 809 (31%) of the 2,578 survivors assigned to NCSI LEVEL 3 were on regular hospital follow-up even though the recommended type of follow-up associated with this Level is regular hospital multi-disciplinary team review. This percentage declined with age from 57% to 16% among survivors aged under 20 years to survivors aged at least 50 years, respectively. 1,388 (79%) of the 1,769 not on hospital follow-up were survivors of a CNS tumour (40%), Hodgkin's lymphoma (20%) and Wilms' tumour (19%). The decline in the percentage on regular long-term hospital follow-up with increased attained age for survivors of each of these three childhood cancers is provided in Figures 2.3a, 2.3b, 2.3c; in particular the percentage for CNS tumour declined from 61% to 19% for those aged under 20 years to those aged at least 50 years, respectively. Overall, 453 (52%) of 874 of ALL survivors were on hospital follow-up and this percentage declined with age from 75% to 27% among those aged under 20 years to those survivors aged at least 30 years, respectively.

2.5 DISCUSSION

2.5.1 Principal findings

This first large scale and population-based assessment of the long-term clinical follow-up status of most adult survivors of childhood cancer in Britain revealed that among survivors within each NCSI Level of care there was a substantial decline in the percentage still on regular hospital follow-up as age of survivor increased. This decline was strongest among survivors within NCSI LEVEL 3, all of whom should be on regular hospital follow-up according to NCSI guidelines: among survivors of all non-leukaemic neoplasms considered together the percentage on hospital follow-up declined from 57% among those aged under 20 years to 16% among those aged at least 50 years; among survivors of acute lymphoblastic leukaemia the percentage on regular long-term hospital follow-up declined from 75% among those aged under 20 years to 27% among those aged at least 30 years. There is a need for clinical review of those NCSI LEVEL 3 survivors who are not on hospital follow-up with consideration given to potential recall to the NHS and we give a detailed justification for this proposal below.

Others have observed that among survivors of adult cancer the level of long-term clinical follow-up of cancer survivors should involve consideration of risk stratification (175). Other studies of survivors of childhood cancer in North America (176), Sweden (177), Switzerland (178) and in the UK (156, 162) have shown that older age and longer time from diagnosis were associated with a decline in survivors being on regular hospital follow-up or a decrease in reporting an outpatient cancer related visit or a visit to a cancer centre. Conversely, there is evidence from one study of the likelihood of seeing an oncologist being elevated with increasing age of childhood, adolescent and young adult survivor, although the survivors in this study are on average comparatively young (mean age 25.5 years) (179).

When looking at the variation of survivors on long-term hospital follow-up by geographical region, childhood cancer survivors were more likely to be on follow-up in the North West than in London. Historically the North West is known to have principal treatment centres with clinicians actively involved in the long-term hospital follow-up of childhood cancer survivors once childhood cancer survivors have completed their treatment and reached five-year survival. Yorkshire and Humber, the West Midlands and Scotland are also regions where childhood cancer research is particularly active which may be a possible explanation as to survivors being more likely than childhood cancer survivors in London of being on long-term hospital follow-up.

The variation of long-term hospital follow-up by cancer diagnosis may be explained by several reasons; the number of leukaemia survivors began to increase considerably from 1975 and as a group are much younger and diagnosed more recently than other survivor groups in the BCCSS thus this would increase the extent to which they are followed-up in a hospital (156). Another possible reason could be the complexity of care required by the survivor group and the risk of adverse late effects, for instance CNS tumour survivors often require specialist care not only by oncologists but from neurosurgeons, endocrinologists and neurologists as well. Thus such survivors may be discharged from paediatric oncologists but then followed-up by other specialist consultants within a hospital setting.

2.5.2 NCSI LEVEL 3 survivors not on hospital follow-up

Of the non-leukaemic survivors assigned to NCSI LEVEL 3, only 31% were on regular long-term hospital follow-up. For leukaemia survivors 52% of those assigned to NCSI LEVEL 3 were on hospital follow-up, but relatively few were aged over 30 years. A recent Scottish study, which assigned childhood cancer survivors to levels of clinical follow-up using the

Scottish Intercollegiate Guidelines Network (SIGN), found that the percentage of survivors on regular hospital follow-up rose with increasing SIGN level of follow-up assigned: 34%, 50% and 66% for those assigned to Level 1, 2 and 3, respectively. The considerable difference between the results for this one Scottish centre and the whole of England, Wales and Scotland could be explained by a number of factors including that their survivors were much younger (median age 19 years), treated more recently, and this centre has a long history of research in survivorship issues and therefore it would not be surprising if their levels of clinical follow-up were higher than average across Britain (180).

Exploring the composition of the non-leukaemic survivors assigned to NCSI follow-up LEVEL 3 revealed that 79% of the survivors not on regular long-term hospital follow-up had been treated for a CNS neoplasm (40%), Hodgkin lymphoma (20%) or Wilms' tumour (19%). Similarly, Edgar *et al* (2012), reported that of the childhood cancer survivors not on regular hospital follow-up, survivors of a CNS neoplasm were one of the most frequent primary diagnoses (180). There is evidence that survivors of a CNS neoplasm, Wilms' tumour, and Hodgkin's lymphoma, especially if treated with radiotherapy, are at an increased risk of adverse physical health late effects (121, 164). CNS tumour survivors who have received radiotherapy, for example, are at increased risk from late death due to recurrence (100), subsequent primary neoplasms (63, 181), stroke (110, 182) and endocrine problems such as those relating to growth (76), sexual development (183) and thyroid function (77, 78). Hodgkin lymphoma survivors who have received radiotherapy are at an increased risk of developing breast cancer (63, 184-187), heart disease (72, 188) and pulmonary conditions (93). Wilms' tumour survivors who have received radiotherapy are at increased risk of cardiovascular disease such as hypertension and cardiac problems (73, 189), subsequent primary neoplasms (63) and infertility (88, 190). Previously irradiated female Wilms' tumour

survivors are also at increased risk of reproductive problems and adverse pregnancy outcomes (88, 191). In addition to physical health outcomes survivors of CNS tumours treated with radiotherapy, also experience excess risks of psychosocial problems including higher levels of cognitive problems than survivors of other childhood cancer types (97) and achieve lower than expected educational attainment (128). Such evidence justifies that serious consideration be given to systems for the recall to the NHS of such LEVEL 3 survivors who are not on regular long-term hospital follow-up.

2.5.3 NCSI LEVEL 1 survivors on follow-up who may not need to be on follow-up

Of the survivors assigned to NCSI LEVEL 1, 12% of non-leukaemia survivors and 66% of leukaemia survivors were still on regular long-term hospital follow-up. The NCSI proposes that survivors assigned to LEVEL 1 are likely to be safe to self-manage their own care (155) thus an assessment needs to be made as to whether less intrusive clinical follow-up for survivors within NCSI LEVEL 1 would be justified. Other studies have also suggested that many survivors receive more intense follow-up than necessary given their estimated level of risk (42).

2.5.4 GPs willingness to be involved in long-term follow-up of childhood cancer survivors

The overall proportion of general practitioners who were willing to discuss personal medical questions with childhood cancer survivors relating to survivorship and late consequences of treatment was relatively high at 74%. This finding is encouraging as it is anticipated that GPs are likely to be one of the groups of health care professionals who might take on more responsibility for the long-term clinical care of increasing numbers of childhood cancer survivors, particularly those survivors assigned to NCSI LEVEL 2 (155). In support of such a change, a Dutch study has shown the willingness of GPs to participate in the follow-up care of survivors when there was a shared model of care between hospital clinicians and

community doctors; 97% of the GPs surveyed agreed to participate (192). The CCSS reported that 85% of primary care physicians whom they surveyed with respect to their preference of model of care of childhood cancer survivors preferred to care for such survivors alongside a cancer-based physician or within a well-defined long-term follow-up program (193). These findings of others taken together with those reported here relating to GP willingness to be involved in follow-up care of childhood cancer survivors are encouraging from the perspective of their increased involvement. An advantage that has been noted by clinicians is that long-term follow-up care provided by GPs would enable cancer specialists to focus more on acute care; additionally GPs could refer a survivor back to specialist centres with relative ease should this be required (194). However some childhood cancer survivors have reported that they feel that GP-led follow-up is not appropriate as they lack specialist knowledge and have been considered less favourably to hospital-based forms of follow-up (162, 195). It is critically important that there needs to be improved communication between primary and secondary care providers and child and adult services for follow-up to work in the primary care setting; in addition to improved training of GPs in survivorship issues, as already observed by others (156, 193, 196-200).

2.5.5 Study limitations

As well as the considerable strengths of having an underlying population-based cohort, large numbers relating to almost all adult survivors of childhood cancer in Britain and reliable estimates of risk relating to survivors aged up to 50 years, there are some limitations inherent in our investigation. There are potential uncertainties in the replies generated from the GPs who completed the questionnaire in being representative of all such GPs within the UK. However the high response rate from the GPs approached with the survey at 91% suggests that this may not be too much of an issue here. Another limitation of our study is the way in

which the question of willingness was put to GPs, the question asked whether GPs would be prepared to discuss with the patient medical questions which might arise from the BCCSS questionnaire and not whether they would be content to become involved in survivor follow-up on a regular basis.

2.5.6 Conclusions

The NCSI has proposed substantial changes to clinical follow-up practices within the NHS for the future, but until now there was no evidence relating to the clinical follow-up status of most adult survivors of cancer in childhood or young adulthood throughout Britain. Changes proposed are a move away from a one-size fits all model of follow-up towards risk stratification, whereby the level of care to be offered corresponds to the anticipated level of risk of serious adverse health outcomes (155). The excess risks of serious adverse health outcomes in childhood cancer survivors still persist 45 years from diagnosis of the original cancer, such as premature mortality and the development of a subsequent primary neoplasm (55, 63). Our study demonstrates that there is need for consideration of a call back to the NHS of NCSI LEVEL 3 survivors who are not currently on long-term hospital follow-up. In contrast survivors assigned to NCSI LEVEL 1 who are still on long-term hospital follow-up should be reviewed for consideration of whether less intensive clinical follow-up would be safe and more appropriate to their estimated risks of adverse health outcomes.

Table 2.1 Number (%) of childhood cancer survivors on hospital follow-up and General Practitioners willing to provide advice to childhood cancer survivors; with odds ratios and 95% confidence intervals from logistic regression models associated with specified demographic, cancer and treatment potential explanatory factors

	Factor	No.	No. of survivors on follow-up (%)	Unadjusted OR (95%CI)	OR (95% CI)	No. of GPs willing to provide advice (%)	Unadjusted OR (95%CI)	OR (95% CI)
Overall totals		12978	4707 (36.3)			9595 (73.9)		
Sex	Male	7045	2562 (36.4)	1.00 (referent)	1.00 (referent) †	5100 (72.4)	1.00 (referent)	1.00 (referent) †
	Female	5933	2145 (36.2)	0.99 (0.92 to 1.06)	1.05 (0.97 to 1.14)	4495 (75.8)	1.19 (1.10 to 1.29)	1.20 (1.10 to 1.30)
	P heterogeneity			0.802	0.206		<0.001	<0.001
Attained age, y	<20	2620	1635 (62.4)	1.00 (referent)	1.00 (referent) †	1956 (74.7)	1.00 (referent)	1.00 (referent) †
	20-29	4603	1929 (41.9)	0.43 (0.39 to 0.48)	0.36 (0.32 to 0.40)	3421 (74.3)	0.98 (0.88 to 1.10)	0.97 (0.86 to 1.09)
	30-39	3664	912 (25.0)	0.20 (0.18 to 0.22)	0.15 (0.14 to 0.17)	2679 (73.1)	0.92 (0.82 to 1.04)	0.93 (0.82 to 1.05)
	40-49	1487	175 (11.8)	0.08 (0.07 to 0.10)	0.06 (0.05 to 0.08)	1086 (73.0)	0.92 (0.80 to 1.06)	0.95 (0.81 to 1.11)
	≥50	604	56 (9.3)	0.06 (0.05 to 0.08)	0.04 (0.03 to 0.06)	453 (75.0)	1.02 (0.83 to 1.25)	1.06 (0.85 to 1.32)
	P trend			<0.001Δ	<0.001Δ		0.296Δ	0.753Δ
Childhood cancer type	Wilms' tumour	1177	429 (36.5)	1.00 (referent)	1.00 (referent)†	877 (74.5)	1.00 (referent)	1.00 (referent) †
	Leukaemia	3531	1664(47.1)	1.55 (1.35 to 1.78)	1.21 (1.04 to 1.41)	2666 (75.5)	1.05 (0.91 to 1.23)	1.05 (0.90 to 1.23)
	Hodgkin's lymphoma	936	330 (35.2)	0.95 (0.79 to 1.13)	1.28 (1.04 to 1.57)	684 (73.0)	0.92 (0.76 to 1.12)	0.98 (0.80 to 1.21)
	NHL	690	266 (38.5)	1.09 (0.90 to 1.32)	1.21 (0.98 to 1.51)	506 (73.2)	0.94 (0.76 to 1.16)	0.98 (0.79 to 1.23)
	CNS neoplasms	2667	919 (34.5)	0.92 (0.79 to 1.06)	1.14(0.97 to 1.34)	1916 (71.9)	0.87 (0.75 to 1.02)	0.87 (0.74 to 1.03)
	Neuroblastoma	549	179 (32.6)	0.84 (0.68 to 1.05)	0.69 (0.55 to 0.88)	405 (73.8)	0.96 (0.76 to 1.21)	0.99 (0.78 to 1.25)
	Retinoblastoma (heritable)	385	108 (28.1)	0.70 (0.53 to 0.87)	0.85 (0.64 to 1.12)	269 (70.0)	0.79 (0.62 to 1.02)	0.81 (0.63 to 1.05)
	Retinoblastoma (non-heritable)	531	59 (11.1)	0.22 (0.16 to 0.29)	0.23 (0.17 to 0.31)	393 (74.0)	0.97 (0.77 to 1.23)	0.97 (0.77 to 1.23)
	Bone sarcoma	472	170 (36.2)	0.98 (0.79 to 1.22)	1.23 (0.95 to 1.58)	370 (78.4)	1.24 (0.96 to 1.60)	1.30 (0.99 to 1.70)
	STS	897	272 (30.3)	0.76 (0.63 to 0.91)	0.82(0.67 to 1.01)	665 (74.1)	0.98 (0.80 to 1.20)	1.00(0.82 to 1.23)
	Other neoplasms	1143	311 (27.2)	0.65 (0.55 to 0.78)	0.69 (0.56 to 0.84)	844 (73.9)	0.97 (0.80 to 1.17)	0.98 (0.80 to 1.19)
	P heterogeneity			<0.001	<0.001		0.0347	0.036
Age at childhood cancer diagnosis, y	0-4	6118	2368 (38.7)	1.00 (referent)	1.00 (referent) †	4516 (73.8)	1.00 (referent)	1.00 (referent) †
	5-9	3436	1265 (36.8)	0.92 (0.85 to 1.00)	1.17 (1.06 to 1.30)	2580 (75.1)	1.07 (0.97 to 1.18)	1.08 (0.97 to 1.20)
	10-14	3424	1074 (31.4)	0.72 (0.66 to 0.79)	1.49 (1.32 to 1.68)	2499 (73.0)	0.96 (0.87 to 1.05)	0.97 (0.86 to 1.09)
	P trend			<0.001Δ	<0.001Δ		0.544Δ	0.720Δ
Chemotherapy	No	4056	821 (20.2)	1.00 (referent)	1.00 (referent)*	3005 (74.1)	1.00 (referent)	1.00 (referent)*
	Yes	4702	1760 (37.4)	2.36 (2.14 to 2.60)	1.40 (1.23 to 1.61)	3489 (74.2)	1.01 (0.91 to 1.11)	1.00 (0.87 to 1.13)
	P heterogeneity			<0.001	<0.001		0.903	0.947
Surgery	No	4162	1519 (36.5)	1.00 (referent)	1.00 (referent)*	3095 (74.4)	1.00 (referent)	1.00 (referent)*
	Yes	5152	1148 (22.3)	0.50 (0.46 to 0.55)	1.02 (0.89 to 1.16)	3788 (73.5)	0.96 (0.87 to 1.05)	0.93 (0.82 to 1.06)
	P heterogeneity			<0.001	0.819		0.360	0.302
Radiotherapy	No RT	2796	625 (22.4)	1.00 (referent)	1.00 (referent)*	2081 (74.4)	1.00 (referent)	1.00 (referent)*
	RT which excluded the head and abdomen	1602	418 (25.8)	1.21 (1.05 to1.39)	1.45 (1.23 to 1.71)	1197 (73.8)	0.97 (0.84 to 1.11)	0.97 (0.83 to 1.13)
	RT to an abdominal site	1123	235 (20.9)	0.92 (0.78 to 1.09)	1.00 (0.83 to 1.22)	831 (74.0)	0.98 (0.83 to 1.15)	0.99 (0.83 to 1.18)
	RT to the head	3591	1408 (39.2)	2.24 (2.00 to 2.50)	1.76 (1.54 to 2.03)	2655 (73.9)	0.97 (0.87 to1.09)	0.96 (0.84 to 1.09)
	P heterogeneity			<0.001	<0.001		0.963	0.930
Region	London	1247	424 (34.0)	1.00 (referent)	1.00 (referent)†	879 (70.5)	1.00 (referent)	1.00 (referent)†
	North East	607	210 (34.6)	1.03 (0.84 to 1.26)	0.99 (0.80 to 1.24)	474 (78.1)	1.49 (1.19 to1.87)	1.50 (1.19 to 1.88)
	North West	1543	711 (46.1)	1.66 (1.42 to 1.94)	1.86 (1.58 to 2.21)	1138 (73.8)	1.18 (1.00 to 1.39)	1.19 (1.00 to 1.40)
	Yorkshire and Humber	1138	459 (40.3)	1.31 (1.11 to 1.55)	1.19 (0.99 to 1.42)	823 (72.3)	1.09 (0.92 to 1.31)	1.09 (0.91 to 1.31)
	East Midlands	969	330 (34.1)	1.00 (0.84 to 1.20)	0.97 (0.80 to 1.18)	702 (72.5)	1.10 (0.91 to 1.33)	1.09 (0.91 to 1.32)
	West Midlands	1218	496 (40.7)	1.33 (1.13 to 1.57)	1.37 (1.15 to 1.64)	875 (71.8)	1.07 (0.90 to 1.27)	1.07 (0.90 to 1.27)
	East England	1304	408 (31.3)	0.88 (0.75 to 1.04)	0.91 (0.76 to 1.09)	937 (71.9)	1.07 (0.90 to 1.27)	1.08 (0.91 to 1.28)
	South East	1809	571 (31.6)	0.90 (0.77 to 1.04)	0.87 (0.74 to 1.03)	1383 (76.5)	1.36 (1.15 to 1.60)	1.37 (1.16 to 1.61)
	South West	1269	397 (31.3)	0.88 (0.75 to 1.04)	0.87 (0.72 to 1.04)	956 (75.3)	1.28 (1.07 to 1.53)	1.29 (1.08 to 1.54)
	Wales	663	230 (34.7)	1.03 (0.85 to 1.26)	1.03 (0.83 to 1.28)	498 (75.1)	1.26 (1.02 to 1.57)	1.26 (1.02 to 1.57)
	Scotland	1128	444 (39.4)	1.26 (1.07 to 1.49)	1.32 (1.10 to 1.58)	867 (76.9)	1.39 (1.16 to 1.67)	1.40 (1.17 to 1.69)
	P heterogeneity			<0.001	<0.001		<0.001	<0.001
NCSI Levels	NCSI Level 1	1182	221 (18.7)	1.00 (referent)	1.00 (referent)§	917 (77.6)	1.00 (referent)	1.00 (referent)§
	NCSI Level 2	3443	1073 (31.2)	1.97 (1.67 to 2.32)	1.88 (1.57 to 2.25)	2550 (74.1)	0.83 (0.71 to 0.97)	0.82 (0.70 to 0.96)
	NCSI Level 3	8077	1262 (36.6)	2.51 (2.13 to 2.95)	2.68 (2.24 to 3.20)	2515 (72.9)	0.78 (0.66 to 0.91)	0.77 (0.66 to 0.91)
	P heterogeneity		<0.001	<0.001	<0.001		0.005	0.006

CNS = central nervous system; CI = confidence interval; NCSI= National Cancer Survivorship Initiative, NHL= Non-Hodgkin's Lymphoma; OR = odds ratio; STS = soft tissue sarcomas; RT= radiotherapy, y= years

† The multivariate model for these factors included the following; sex; attained age; childhood cancer type; age at childhood cancer diagnosis; region (main model without treatment).

* The multivariate model for these factors included the following; sex, attained age, age at childhood cancer diagnosis, chemotherapy, surgery, radiotherapy according to site of treatment (treatment model).

§ The multivariate model for these factors included the following; sex, attained age, age at childhood cancer diagnosis, region, NCSI Levels (model excluding treatment and cancer diagnosis)

ΔThe p value for test for trends are reported here, in addition tests for non-linearity were conducted.

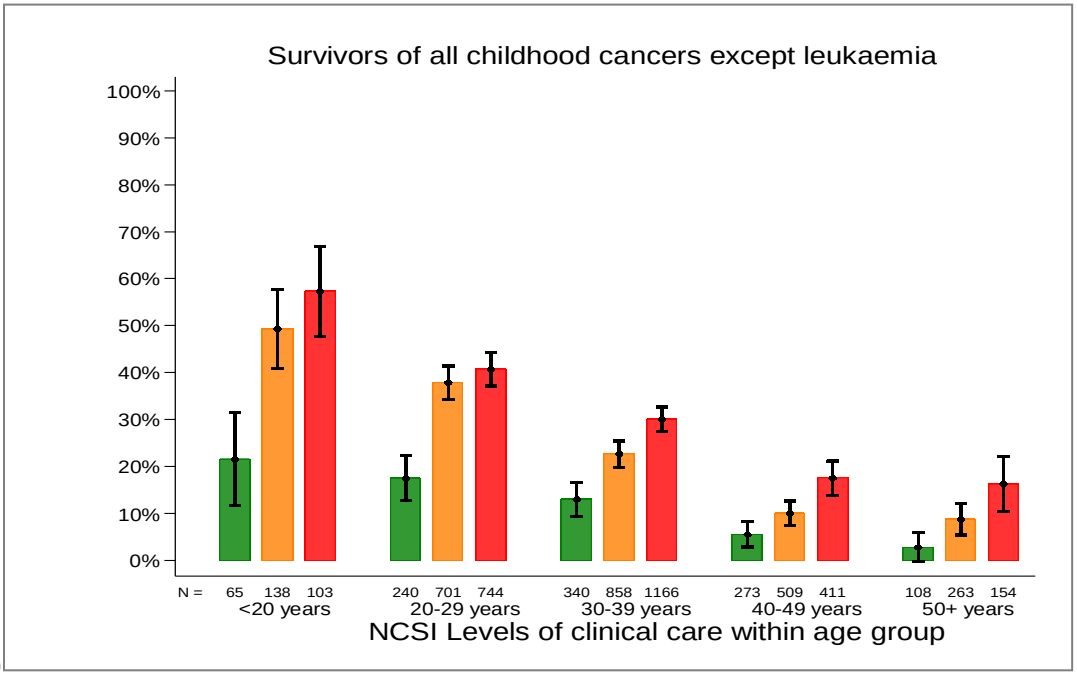
Figure 2.1 National Cancer Survivorship Initiative Levels of clinical follow-up defined in terms of type of childhood cancer and treatment received

	Type of Childhood Cancer									
	HODG	NHL	CNS	NEURO	RETINO (HER)	RETINO (NON-HERITABLE)	WILMS	BONE	STS	OTHER
S alone	1	1	2	1	2	1	1	1	1	1
R alone	3	2	3	2	3	2	2	2	2	2
C alone	2	2	2	2	2	1	2	2	2	2
S + R	3	2	3	2	3	2	2	2	2	2
S + C	2	2	2	2	2	1	2	2	2	2
R + C	3	2	3	3	3	2	3	3	3	2
S + R + C	3	2	3	3	3	2	3	3	3	2

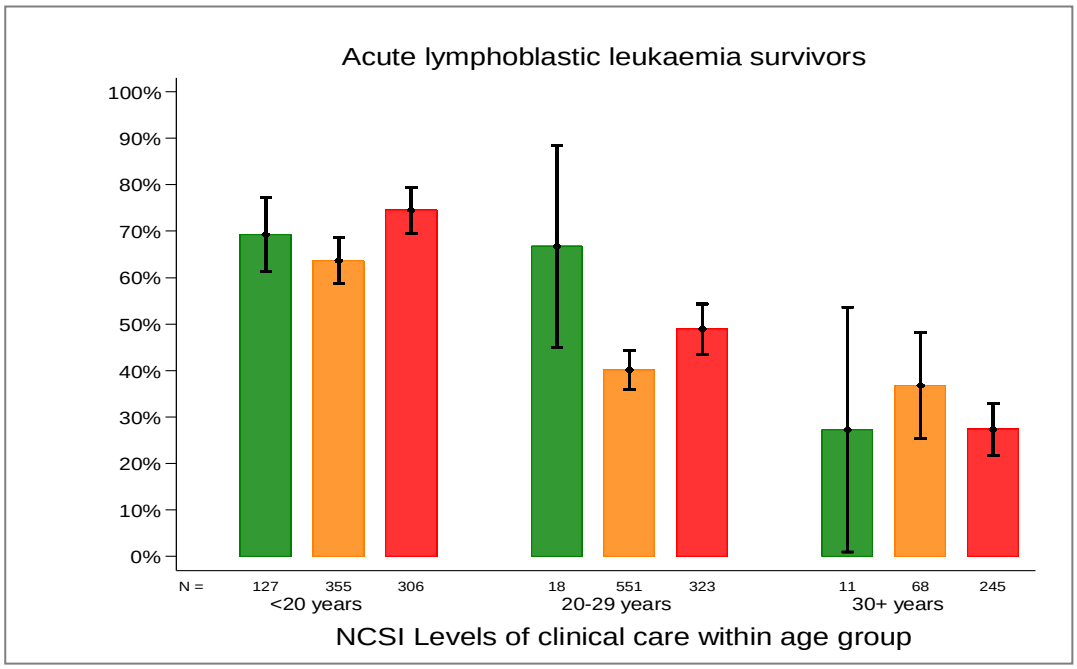
CNS - Central Nervous System; C - Chemotherapy; HODG - Hodgkin's lymphoma; NHL - Non-Hodgkin's lymphoma; NEURO - Neuroblastoma ; RETINO - Retinoblastoma; STS - Soft tissue sarcoma; S - Surgery; R - Radiotherapy;

Figure 2.2 Extent of regular long-term hospital follow-up among survivors by age for each National Cancer Survivorship Initiative Levels of clinical follow-up a) among all childhood cancers except leukaemia, b) among acute lymphoblastic leukaemia survivors

a)



b)



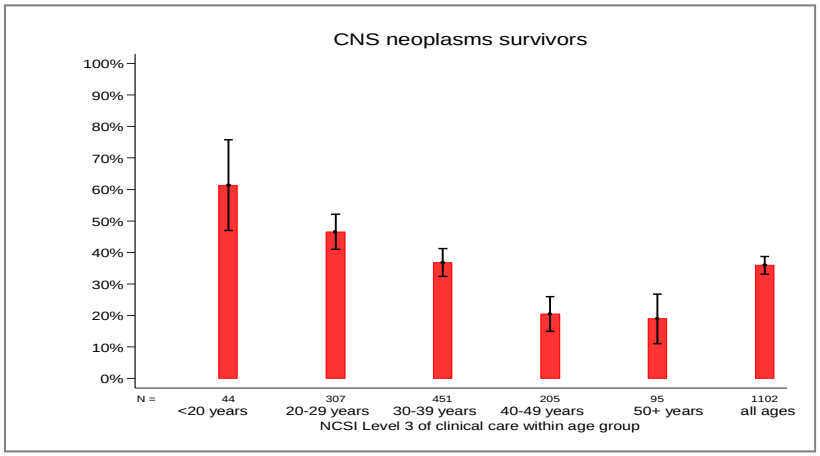
NCSI LEVEL 1

NCSI LEVEL 2

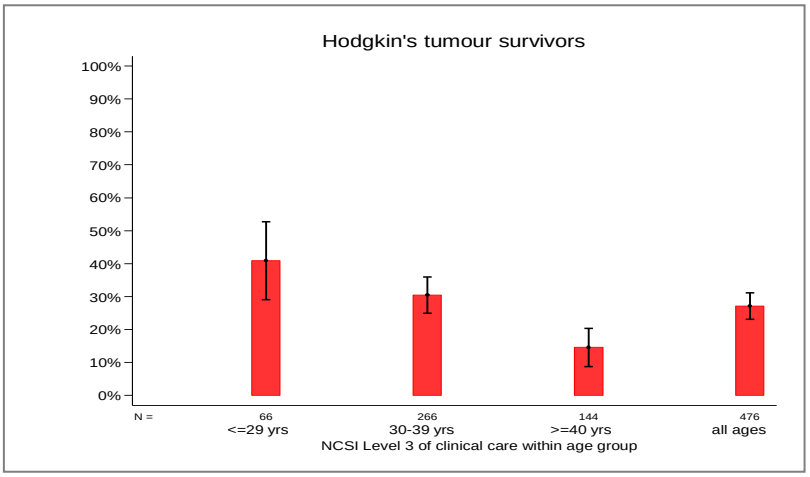
NCSI LEVEL 3

Figure 2.3 Extent of regular long-term hospital follow-up among survivors of specific types of childhood cancer assigned to the National Cancer Survivorship Initiative LEVEL 3 of clinical follow-up care in relation to attained age, a) CNS neoplasms survivors b) Hodgkin's tumour survivors, c) Wilm's tumour survivors

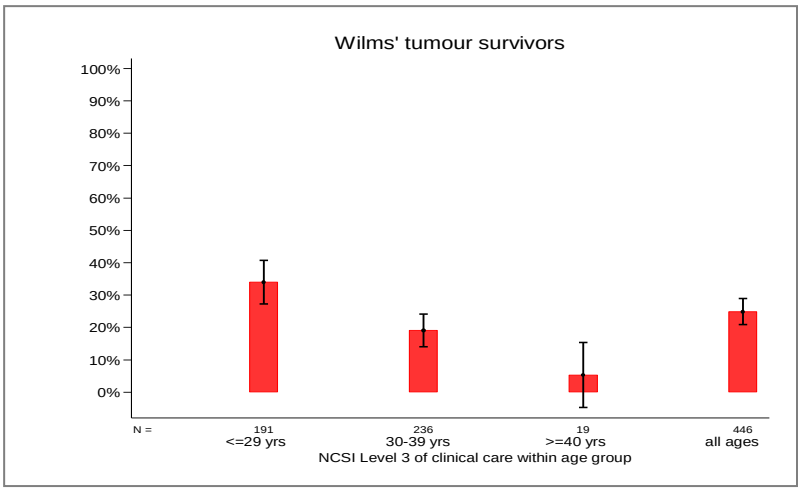
a)



b)



c)



CHAPTER 3 ADVERSE HEALTH AND SOCIAL OUTCOMES IN LONG-TERM SURVIVORS OF A CENTRAL NERVOUS SYSTEM TUMOUR: THE BRITISH CHILDHOOD CANCER SURVIVOR STUDY

3.1 ABSTRACT

Background: To our knowledge, no study has investigated the risks of adverse health outcomes beyond 30 years from diagnosis of specific childhood Central Nervous System (CNS) tumours. We investigated such risks, specifically following craniopharyngioma, medulloblastoma and astrocytoma.

Methods: The BCCSS included 4,111 five-year survivors of a CNS tumour. We investigated cause-specific mortality and risk of subsequent primary neoplasms (SPNs). Among survivors who returned a questionnaire, smoking, drinking, education, marriage, body mass index, health care use and health-status (SF-36) were compared to that expected from the general population.

Results: Between 30 and 50 years from diagnosis the principal causes of death accounting for most of the total excess deaths observed were: after craniopharyngioma, recurrence (28%) and circulatory (35%); after medulloblastoma, recurrence (20%) and SPN (48%); after astrocytoma, recurrence (35%), SPN (13%) and respiratory (13%). Consequently, CNS subtype was a strong risk stratification factor, as was cranial/craniospinal radiotherapy in that, of the total excess number of deaths observed beyond 30 years from diagnosis among those exposed (unexposed) to radiotherapy 21% (3%) and 11% (0%) were attributable to SPN and stroke respectively. The cumulative risks of developing a meningioma by 35 years from diagnosis among those exposed (unexposed) to radiotherapy were 3.9% (0.6%). Educational attainment and marriage showed greater deficits among those CNS tumour survivors who had received cranial/craniospinal irradiation.

Conclusion: CNS subtype and cranial irradiation provide strong risk stratification factors which may be used in long-term follow-up clinics to powerfully discriminate between groups of survivors in terms of anticipated risk of serious adverse health outcomes.

3.2 INTRODUCTION

Previous studies have reported increased risks of a range of adverse health and social outcomes among long-term central nervous system (CNS) tumour survivors including premature mortality, subsequent primary neoplasms (SPNs) and a spectrum of non-neoplastic conditions (61, 76, 97, 99, 100, 183, 201). However, previous studies have either investigated outcomes of all CNS tumours considered together and quantified risks beyond 30 years from diagnosis, or have investigated specific CNS tumour subtypes (subsequently referred to as CNS subtype) and quantified risks up to 30 years from diagnosis.

The objective of this study was to quantify the risks of adverse health and social outcomes amongst CNS tumour survivors overall and by CNS subtype, specifically craniopharyngioma, medulloblastoma and astrocytoma, both before and after 30 years from diagnosis.

3.3 METHODS

3.3.1 British Childhood Cancer Survivor Study

The British Childhood Cancer Survivor Study (BCCSS) is a large scale population-based cohort study established to investigate the long-term adverse health and social outcomes of childhood cancer and its treatment (30). The BCCSS cohort includes 17,980 individuals diagnosed with childhood cancer between 1940 and 1991 inclusive, before age 15 years, in Great Britain and who survived for at least five years. This includes 4,111 (22.9%) survivors diagnosed with a CNS neoplasm. The BCCSS cohort was identified using the population-based National Registry of Childhood Tumours. Ethical approval for the BCCSS was obtained from the relevant Multi-Centre Research Ethics Committee and every Local Research Ethics Committee in Britain.

3.3.2 Ascertainment of deaths and subsequent primary neoplasms

Death ascertainment was through electronic record linkage of the BCCSS cohort, via the Health and Social Care Information Centre (HSCIC), to the national population-based death registration system which enables ascertainment of vital and emigration status of each cohort member (55). SPN ascertainment was through record linkage with the population-based national cancer registry via HSCIC. All SPNs were validated by obtaining copies of diagnostic reports, particularly pathology reports confirming site, type and date of diagnosis (63).

3.3.3 BCCSS Questionnaire

All survivors who were alive and aged at least 16 years were sent a 40-page BCCSS questionnaire via their general practitioner: 3,054 CNS survivors were thus eligible and 2,222 (72.8%) returned a completed BCCSS questionnaire (30). This questionnaire is shown in Appendix 8.2.

3.3.4 CNS neoplasm classification

CNS neoplasms were classified into subtypes: craniopharyngioma, medulloblastoma, astrocytoma and other diagnoses using the morphology classification of the International Classification of Diseases for Oncology (ICD-O-3) (14).

3.3.5 Statistical methods

Cause-specific mortality

Follow-up started at five years after diagnosis of the CNS tumour and ended on 31st December 2010 with earlier exits at death or emigration. Standardised mortality ratios (SMRs) and absolute excess risks (AERs) were calculated for specific causes of death. The SMR was defined as the ratio of the observed to expected number of deaths, the AER as the observed minus expected number of deaths divided by the person-years at risk multiplied by

10,000. Cumulative mortality for specific causes of death after specific CNS subtypes was estimated, with other causes of death treated as competing risks.

Subsequent Primary Neoplasms

Entry to risk was again at five-year survival and ended at the first occurrence of diagnosis of a SPN, emigration, death or reaching 31st December 2006. Standardised incidence ratios (SIRs) and AERs were calculated as for SMRs and AERs above.

Educational attainment, smoking history and alcohol consumption

Educational attainment, smoking and alcohol consumption comparisons were undertaken between CNS tumour survivors and the national General Household Survey (GHS) (202). Odds Ratios (ORs) were calculated using a logistic regression model with a generalised estimating equation (GEE) modification, which took into account the clustering present within the GHS sample. Confounding factors were identified a priori and adjustments made as specified in Table 3.6. Four levels of educational attainment were evaluated: degree, teaching qualification, 'A'-level and 'O'-level. The outcome investigated for smoking was the proportion who were current regular smokers. Three outcomes were assessed for alcohol consumption: the prevalence of current drinkers, drinking over weekly recommendations (>21 units/week for men and >14 units/week for women) and consuming harmful amounts of alcohol (>50 units/week for men and >35 units/week for women) (203, 204).

Marital status

The marital status of CNS tumour survivors was compared to that expected from the general population by pooling age-specific ORs using the Mantel-Haenszel method. National marriage registration statistics from the Office for National Statistics (ONS) were used for comparison (205).

Healthcare utilisation

The extent of healthcare utilisation reported by CNS tumour survivors was compared to that expected from the general population using the GHS in relation to four outcomes: (1) talked to a doctor in the last 2 weeks; (2) attended a hospital outpatient department in the last 3 months; (3) hospitalised as a day patient in the last year and; (4) hospitalised as an inpatient in the last year. For each outcome, the OR comparing survivors to the GHS was calculated using a logistic regression model with a GEE modification adjusted for age at questionnaire completion, sex and educational attainment.

Body Mass Index (BMI)

Self-reported height and weight were used to calculate BMI. Overweight was defined as a BMI of ≥25. The BMI of CNS tumour survivors was compared to the general population using the national ONS Omnibus Survey, which involved the collection of self-reported weight and height data for 1804 individuals by interview (206). Separate logistic regressions to calculate ORs of being at least overweight were conducted for males and females, adjusted for age and socio-economic status. A weighting factor was used to take account of the sampling technique used in the Omnibus Survey since only one adult from each selected household was interviewed.

Health status (SF-36)

Functional health and well-being of CNS survivors were investigated using the Short Form (SF-36) health status survey (150). The SF-36 consists of eight scales; physical function, role-physical, role-emotional, social functioning, mental health, vitality, pain and general health perception. The Oxford Healthy Life Survey (OHLS) was used as the general population comparison group (207). For each SF-36 scale, linear regression (adjusted for sex and age at

questionnaire completion) was used to compare the mean scale score of survivors to that of the OHLS population. Direct standardisation was used to compare the percentage of CNS tumour survivors that reported a specific problem or limitation with that expected from the general population.

All analyses were undertaken using Stata 12.1 (Stata Corp, College Station, Texas). Statistical significance was defined as a two-sided p-value less than 0.05.

3.4 RESULTS

3.4.1 Cohort characteristics

Of the 4,111 CNS tumour survivors, 345 (8.4%) had been treated for craniopharyngioma, 632 (15.4%) for medulloblastoma, 2,107 (51.3%) for astrocytoma and 1,027 (25%) for other CNS tumours. The composition of the cohort overall and for those returning a questionnaire, in relation to sex, age at diagnosis, age at questionnaire completion, decade of diagnosis and whether treated with radiotherapy, chemotherapy or surgery is provided in Table 3.1.

3.4.2 Mortality

Deaths after all CNS tumours

Observed mortality after all CNS tumours was 13-times that expected, with an excess of 118 deaths per 10,000 person-years. Substantial excesses (observed≥50 and SMR≥5) were observed for deaths from SPN, circulatory and respiratory disease (Table 3.2). Prior to 30 years from diagnosis, 75% of excess deaths were attributable to recurrence, whilst beyond 30 years from diagnosis only 31% of excess deaths were attributable to recurrence (Table 3.3). Comparing CNS tumour survivors who had (had not) received cranial/craniospinal radiotherapy, revealed that beyond 30 years from diagnosis 21% (3%) of excess deaths were attributable to SPN and 11% (0.2%) were attributable to stroke (Table 3.3). Beyond 30 years

from diagnosis 12 to 13% of excess deaths were attributable to respiratory causes, irrespective of treatment with radiotherapy.

Deaths after medulloblastoma

Survivors of a medulloblastoma had the highest overall excess mortality of the three CNS subtypes, 21-times that expected (Table 3.2). Before 30 years from diagnosis, 75% of excess deaths were attributable to recurrence compared to 20% after 30 years, when the largest proportion of excess deaths was attributable to SPNs (48%) (Table 3.4). The cumulative risk of death from SPN and non-neoplastic causes were both substantial by 50 years from diagnosis at 16% and 17% respectively, Figure 3.1. The expected cumulative risk from all causes was 7% at 50 years of follow-up.

Deaths after craniopharyngioma

Mortality among survivors of a craniopharyngioma was 20-times that expected (Table 3.2). Before 30 years from diagnosis 69% of the total excess deaths were attributable to recurrence, whereas beyond 30 years only 28% of excess deaths were attributable to recurrence and 35% were attributable to circulatory causes (Table 3.4). Cumulative risk of a non-neoplastic death by 50 years was 33.3%, whilst the corresponding risk of SPN death was only 2%, as shown in Figure 3.1. The expected cumulative risk from all causes was 8% at 50 years of follow-up.

Deaths after astrocytoma

Among astrocytoma survivors, the SMR for all causes of death was 11-times that expected (Table 3.2). Beyond 30 years of follow-up, the main causes of death that accounted for the greatest excess numbers observed were recurrence (35%), SPN (13%) and respiratory (13%) (Table 3.4). Astrocytoma survivors had a similar cumulative risk of non-neoplastic death by 50 years of follow-up to medulloblastoma survivors (15% compared to 17%). However, in

contrast corresponding risks of SPN death were dissimilar at 6% and 16%, respectively, Figure 3.1. The cumulative risk of death from recurrence by 50 years of follow-up was 19.8%. The expected cumulative risk for all causes was 7.4% at 50 years of follow-up.

3.4.3 Incidence of Subsequent Primary Neoplasms

Overall, CNS tumour survivors were 3-times more likely than expected to develop a SPN: with an excess of 12 SPNs per 10,000 person-years (Table 3.5). The cumulative risk of developing any SPN by 35 years from CNS tumour diagnosis was 4.5% (Figure 3.2). By the same time, the cumulative risk of developing a meningioma SPN was greater for survivors exposed to cranial/craniospinal irradiation (3.9%) than among those unexposed (0.6%) P<0.0001 (Figure 3.2). The cumulative risk of developing a glioma SPN by 35 years from CNS tumour diagnosis was 2.1% among those survivors treated with cranial/craniospinal radiotherapy, whilst 0.6% among those not so treated P<0.0001 (Figure 3.2). Medulloblastoma survivors had an 8-fold increased risk of developing any SPN. The excess risk was particularly high for developing a glioma (SIR=43.4, 95%CI:24.6-76.4). The risk of developing any SPN among astrocytoma survivors was 2-fold (SIR=2.3, 95%CI:1.9-2.9) (Table 3.5).

3.4.4 Education attainment, smoking, alcohol consumption, marriage, health care use and BMI (Table 3.6)

CNS tumour survivors were found to experience large deficits in their educational attainment at all levels compared to that expected. The ORs compared with expected educational attainment across the four levels was 0.3-0.5 in CNS survivors who received cranial/craniospinal radiotherapy; and 0.6-0.7 in CNS survivors who did not. Of all subtypes, medulloblastoma survivors were least likely to attain any of the four qualifications (ORs=0.3-0.4), but all subtypes had substantial deficits in some levels of educational attainment. The

above ORs may be approximately interpreted as relative risks, but because the outcome is common (>10%) the relative risks may be exaggerated somewhat (208).

Compared to the general population, CNS subtypes were significantly less likely to be current regular smokers (medulloblastoma and craniopharyngioma, both OR=0.2, 95%CI:0.1-0.3; astrocytoma, OR=0.4, 95%CI:0.3-0.5) or consume alcohol over the weekly recommendations (craniopharyngioma: OR=0.4, 95%CI:0.2-0.8; medulloblastoma: OR=0.2, 95%CI:0.1-0.4; astrocytoma: OR=0.6, 95%CI:0.5-0.7).

CNS tumour survivors, particularly male survivors (OR=0.2, 95%CI:0.2-0.3), were significantly less likely to have married compared to the general population. Male medulloblastoma survivors were the least likely to have married (OR=0.1, 95%CI:0.1-0.2) compared to the general population.

Compared to the general population, CNS tumour survivors were more likely to have used healthcare as: an outpatient (OR=3.1, 95%CI:2.7-3.5), inpatient (OR=2.4, 95%CI:2.1-2.8) and day patient (OR=1.6, 95%CI:1.3-1.8). Craniopharyngioma survivors in particular were significantly more likely than expected to visit a hospital as an outpatient (OR=7.0, 95%CI:5.0-9.7) and significantly more likely to be hospitalised as an inpatient (OR=3.6, 95%CI:2.4-5.6).

Each of male and female CNS tumour survivors separately were 2-times more likely than expected to be overweight. Female CNS tumour survivors treated with cranial radiotherapy were 4-times more likely than expected to be overweight. Female craniopharyngioma survivors were 12-times more likely than expected to be overweight, with 84% being classified as overweight.

3.4.5 Health status (SF-36)

CNS tumour survivors overall and within each subtype reported in Table 3.7 scored less favourably than expected on each separate scale of the SF-36; the greatest differences were observed in the physical function, role-physical, social functioning and general health perception scales.

Investigation of the individual items, comprising the physical function scale - Table 3.8, revealed that 48%, 45% and 34% of medulloblastoma, craniopharyngioma and astrocytoma survivors respectively, were limited in 'moderate activities' compared to the 8% expected from the general population. Corresponding percentages for 'climbing one flight of stairs' were 44%, 23% and 24%, respectively, compared with 5% expected and, for 'bathing and dressing yourself' were 20%, 24% and 18%, respectively, compared with 3% expected.

3.5 DISCUSSION

This is the first epidemiological study to have quantified adverse health and social outcomes among survivors of specific types of childhood CNS tumour between 30 and 50 years from the original cancer diagnosis. CNS subtype was a strong risk stratification factor in that it provides strong discrimination in relation to the risk of outcome(s). The cumulative risk of death from all non-neoplastic causes after craniopharyngioma, medulloblastoma and astrocytoma were 33%, 17% and 15%, respectively, by 50 years from diagnosis. The corresponding risks of SPN were 2%, 16% and 6%, respectively. The expected cumulative risk of death from all causes by 50 years from diagnosis was 7 to 8% in relation to each CNS subtype. Beyond 30 years from diagnosis the principal causes of death accounting for most of the total excess numbers observed were: recurrence (28%) and circulatory (35%) after craniopharyngioma; recurrence (20%) and SPN (48%) after medulloblastoma; recurrence (35%), SPN (13%) and respiratory (13%) after astrocytoma. In a previous study, survivors of an astrocytoma were at highest risk of late recurrence 20 years after their original diagnosis

while this study shows that the risk extends beyond 20 years as the cumulative mortality at 50 years was 19.8% (209).

Cranial/craniospinal radiotherapy also emerged as a powerful risk stratification factor. Of the total excess number of deaths observed beyond 30 years from diagnosis among those exposed (unexposed) to cranial/craniospinal radiotherapy, 21% (3%) were attributable to SPN and 11% (0%) to stroke. The cumulative risk of developing a meningioma (the commonest secondary intracranial second neoplasm in this study) by 35 years from diagnosis among those exposed (unexposed) to cranial/craniospinal radiotherapy was 3.9% (0.6%); the corresponding figures for glioma were 2.1% (0.6%). After craniopharyngioma only 3 SPNs were observed and 4.3 were expected. Similar to a previous study, CNS tumour survivors had a 3-fold risk of developing a SPN compared to the general population (100). After medulloblastoma, 50 SPNs were observed, 8-fold expected, while after astrocytoma, 78 SPNs were observed, 2-fold expected. Previous studies have shown an increased risk of SPN development following cranial radiation exposure (60, 61, 210).

Female survivors of craniopharyngioma were almost 12-times more likely than the general population to be overweight or obese. Obesity has been recognised among survivors of craniopharyngioma although this has not been previously quantified in relation to the general population (211-215). Hypothalamic damage with hormonal imbalance is associated with obesity and can also occur as a result of direct invasion by the craniopharyngioma or from surgery or (to a less extent) radiotherapy used in treatment (216-218). Both neurosurgery and cranial radiation for treatment of craniopharyngioma have been identified as risk factors for obesity (121).

In terms of education, all CNS subtypes attained a substantially lower level than expected and medulloblastoma survivors were the most impaired. In a previous study, cranial irradiation has been shown to be the strongest prognostic factor of educational attainment; survivors who had received cranial irradiation were approximately 9-times more likely to have a lower educational level than survivors without cranial irradiation (131). Since medulloblastoma tumours were largely treated with cranial irradiation in this study, this factor is likely to have been influential on their educational attainment. Cranial irradiation could also explain the lowest likelihood of marriage compared to that expected among medulloblastoma survivors compared to other subtypes in our study as the adverse effects of cranial irradiation have been demonstrated in previous studies (100, 142).

CNS tumour survivors overall and by subtype report substantial excess limitations across the SF-36 scale, particularly in the domains of physical function, role-physical, social functioning and general health perception. CNS tumour survivors treated with cranial irradiation had appreciably greater deficits than those not treated with this modality and such deficits have been reported before (219).

3.5.1 Study limitations

Potential limitations of our study include: (i) the level of treatment information available: YES, NO or NO RECORD for each of radiotherapy, chemotherapy and surgery. However, cranial irradiation for brain tumour usually exceeds 30Gy and so having exposed/unexposed is useful for risk stratification. Chemotherapy is rarely used in the treatment of brain tumours except medulloblastoma, but it only became standard care in the mid to late 1990s and such survivors are not included in the present cohort.(ii) Our study questionnaire contained self-reported height and weight, educational attainment, smoking, alcohol consumption, marriage and hospitalisations. However, the general population control data was obtained similarly so

there should be no bias in the comparison. (iii) Survivors were only eligible to receive a study questionnaire if they were alive and aged at least 16 thus there would be a proportion of survivors who were not eligible to receive the questionnaire in the first instance. Survivors who had died before the questionnaire send out may have been treated more aggressively than those survivors who remained alive to receive a questionnaire. Thus caution ought to be exercised in interpreting adverse health and social outcomes ascertained from the BCCSS study questionnaire because of potential selection bias. (iii) Our findings may not be generalisable to children diagnosed with cancer after 1991, but with recent extensions to the BCCSS cohort including those diagnosed from 1992 until 2006 inclusive there will be the opportunity to examine the outcomes addressed in this study in survivors diagnosed in more recent decades who received more modern forms of treatment.

3.5.2 Conclusions

We report the first study to quantify the risks of adverse health and social outcomes among survivors of specific CNS subtypes between 30 and 50 years from diagnosis. In this period of follow-up the principal causes of death accounting for most of the total excess deaths observed were: after craniopharyngioma, recurrence (28%) and circulatory (35%); after medulloblastoma, recurrence (20%) and SPN (48%); after astrocytoma, recurrence (35%), SPN (13%) and respiratory (13%). Consequently CNS subtype is a strong risk stratification factor. Cranial/craniospinal radiotherapy also emerged as a powerful risk stratification factor in that of the total excess number of deaths observed beyond 30 years from diagnosis among those exposed (unexposed) to radiotherapy, 21% (3%) and 11% (0%) were attributable to SPN and stroke respectively. The cumulative risks of developing a meningioma by 35 years from diagnosis among those exposed (unexposed) to radiotherapy were 3.9% (0.6%). Educational attainment and marriage showed greater deficits among those CNS tumour

survivors treated with cranial/craniospinal irradiation. CNS subtype and cranial irradiation provide strong risk stratification factors which may be used in long-term follow-up clinics to discriminate between groups of survivors in terms of anticipated risks of serious adverse health and social outcomes.

Table 3.1 Composition of the CNS cohort overall and for those returning a questionnaire

		Overall BCCSS cohort, n (%)				Questionnaire completed, n (%)			
Characteristic		**All CNS**	**Craniopha-ryngioma**	**Medullo-blastoma**	**Astro-cytoma**	**All CNS**	**Craniopha-ryngioma**	**Medullo-blastoma**	**Astro-cytoma**
Overall		4111	345	632	2107	2222	168	306	1203
Sex	Male	2190 (53.3)	197 (57.1)	385 (60.9)	1044 (49.6)	1156 (52.0)	92 (54.8)	186 (60.8)	590 (49.0)
	Female	1921 (46.7)	148 (42.9)	247 (39.1)	1063 (50.5)	1066 (48.0)	76 (45.2)	120 (39.2)	613 (51.0)
Age at	16-24	n/a	n/a	n/a	n/a	577 (26.0)	39 (23.2)	95 (31.1)	335 (27.9)
Questionnaire	25-34	n/a	n/a	n/a	n/a	721 (32.5)	59 (35.1)	115 (37.6)	370 (30.8)
Completion (y)	35-44	n/a	n/a	n/a	n/a	580 (26.1)	42 (25.0)	64 (20.9)	305 (25.4)
	45-54	n/a	n/a	n/a	n/a	278 (12.5)	22 (13.1)	28 (9.2)	152 (12.6)
	≥55	n/a	n/a	n/a	n/a	66 (3.0)	6 (3.6)	4 (1.3)	41 (3.4)
Age at	0-4	1210 (29.4)	62 (18.0)	190 (30.1)	672 (31.9)	628 (28.3)	25 (14.9)	100 (32.7)	359 (29.8)
Diagnosis (y)	5-9	1510 (36.7)	152 (44.1)	269 (42.6)	738 (35.0)	814 (36.6)	70 (41.7)	131 (42.8)	434 (36.1)
	10-14	1391 (33.8)	131 (38.0)	173 (27.4)	697 (33.1)	780 (35.1)	73 (43.5)	75 (24.5)	410 (34.1)
Decade of	<1970	1218 (29.6)	116 (33.6)	166 (26.3)	610 (29.0)	551 (24.8)	43 (25.6)	60 (19.6)	303 (25.2)
Diagnosis (y)	1970-1979	1243 (30.2)	99 (28.7)	174 (27.5)	635 (30.1)	700 (31.5)	54 (32.1)	92 (30.1)	358 (29.8)
	1980-1991	1650 (40.1)	130 (37.7)	292 (46.2)	862 (40.9)	971 (43.7)	71 (42.3)	154 (50.3)	542 (45.1)
Surgery	No	529 (12.9)	27 (7.8)	43 (6.8)	331 (15.7)	251 (11.3)	14 (8.3)	17 (5.6)	166 (13.8)
	Yes	2897 (70.5)	262 (75.9)	477 (75.4)	1398 (66.4)	1581 (71.1)	124 (73.8)	229 (74.8)	807 (67.1)
	No record	685 (16.7)	56 (16.2)	112 (17.7)	378 (17.9)	390 (17.6)	30 (17.9)	60 (19.6)	230 (19.1)
Chemotherapy	No	2797 (68.0)	251 (72.8)	316 (50.0)	1498 (71.1)	1498 (67.4)	124 (73.8)	134 (43.8)	847 (70.4)
	Yes	291 (7.1)	2 (0.6)	167 (26.4)	61 (2.9)	150 (6.8)	0 (0.0)	88 (28.8)	30 (2.5)
	No record	1023 (24.9)	92 (26.7)	149 (23.6)	548 (26.0)	574 (25.8)	44 (26.2)	84 (27.5)	326 (27.1)
Radiotherapy	No	1115 (27.1)	128 (37.1)	10 (1.6)	720 (34.2)	668 (30.1)	56 (33.3)	7 (2.3)	455 (37.8)
	Yes	2192 (53.3)	143 (41.5)	510 (80.7)	935 (44.4)	1097 (49.4)	77(45.8)	240 (78.4)	469 (39.0)
	No record	804 (19.6)	71 (21.5)	112 (17.7)	452 (21.5)	457 (20.6)	35 (20.8)	59 (19.3)	279 (23.2)

BCCSS: British Childhood Cancer Survivor Study; CNS: central nervous system; NA: not applicable, n: number; y: years

Table 3.2 Standardised Mortality Ratios for CNS tumour survivors overall and CNS subgroups by cause of death

	Obs/Exp	SMR (95%CI)	AER (95%CI)
CNS Overall*			
All causes	1249/98.5	12.7 (12.0-13.4)	117.8 (110.7-124.9)
Infection	12/1.8	6.6 (3.4-11.5)	1.0 (0.3-1.7)
Recurrence∆	776/0.0	NA	79.4 (73.8-85.0)
SPN	149/26.8	5.6 (4.7-6.5)	12.5 (10.1-15.0)
Endocrine	12/2.0	6.1 (3.2-10.7)	1.0 (0.3-1.7)
Nervous system	44/4.1	10.6 (7.7-14.3)	4.1 (2.7-5.4)
Circulatory§	81/17.4	4.7 (3.7-5.8)	6.5 (4.7-8.3)
Cardiac	28/12.5	2.2 (1.5-3.2)	1.6 (0.5-2.6)
Stroke	39/3.4	11.3 (8.1-15.5)	3.6 (2.4-4.9)
Respiratory	70/5.0	14.0 (10.9-17.7)	6.7 (5.0-8.3)
Digestive	13/6.2	2.1 (1.1-3.6)	0.7 (-0.0-1.4)
External	58/28.3	2.1 (1.6-2.7)	3.0 (1.5-4.6)
Other¥	34/6.8	4.9 (3.4-6.9)	2.8 (1.6-3.9)
Craniopharyngioma*			
All causes	149/7.6	19.6 (16.6-23.0)	189.4 (157.4-221.5)
Infection	6/0.1	41.1 (15.1-89.6)	7.8 (1.4-14.3)
Recurrence∆	86/0.0	NA	115.2 (90.9-139.6)
Circulatory§	21/1.3	15.9 (9.8-24.2)	26.4 (14.3-38.4)
Cardiac	6/1.0	6.2 (2.3-13.6)	6.7 (0.3-13.2)
Stroke	9/0.3	35.4 (16.2-67.2)	11.7 (3.8-19.6)
Respiratory	14/0.4	37.6 (20.6-63.1)	18.3 (8.4-28.1)
Medulloblastoma*			
All causes	239/11.1	21.4 (18.8-24.3)	178.3 (154.6-202.0)
Recurrence∆	152/0.0	NA	118.9 (100.0-137.8)
SPN	49/2.5	19.7 (14.5-26.0)	36.4 (25.7-47.1)
Circulatory§	12/1.7	7.0 (3.6-12.2)	8.0 (2.7-13.4)
Respiratory	12/0.5	23.7 (12.3-41.4)	9.0 (3.7-14.3)
Astrocytoma*			
All causes	553/52.9	10.5 (9.6-11.4)	96.0 (87.1-104.8)
Recurrence∆	336/0.0	NA	64.5 (57.6-71.4)
SPN	67/15.1	4.4 (3.4-5.6)	10.0 (6.9-13.0)
Nervous system	23/2.0	10.4 (6.6-15.6)	4.0 (2.2-5.8)
Circulatory§	32/9.5	3.4 (2.3-4.8)	4.3 (2.2-6.4)
Cardiac	14/6.8	2.1 (1.1-3.5)	1.4 (-.0.0-2.8)
Stroke	16/1.9	8.4 (4.8-13.7)	2.7 (1.2-4.2)
Respiratory	27/2.8	9.8 (6.4-14.2)	4.7 (2.7-6.6)
Digestive	8/3.3	2.4 (1.0-4.8)	0.9 (-0.2-2.0)
Perinatal	7/0.9	7.5 (3.0-15.5)	1.2 (0.2-2.2)
External	31/14.4	2.2 (1.5-3.1)	3.2 (1.1-5.3)

AER: absolute excess risks, CNS: central nervous system, CI: confidence interval, Exp: expected, NA: not applicable, Obs: observed, SMR: standardised mortality ratio, SPN: second primary neoplasm

*The causes of death were only included for CNS overall if the number of observed events was >10 and for CNS subtypes if the number of observed events was >5

§For circulatory, this category consists of cardiac, stroke and other cardiovascular conditions; the latter conditions have not been reported

∆Calculation of SMR for deaths due to recurrence would be inappropriate since the expected mortality rate in the general population would be 0. AER for recurrence was calculated as the mortality rate per 10,000 person years

¥ comprises deaths due to blood, mental disorders, musculoskeletal, genitourinary, perinatal and other causes

Table 3.3 Cause of death specific absolute excess risks for CNS tumour survivors overall and by treatment received

Cause of death	Years from diagnosis	CNS overall			CNS overall Cranial RT yes			CNS overall cranial RT no		
		O/E	AER (95%CI)	%	O/E	AER (95%CI)	%	O/E	AER (95%CI)	%
All causes	<30	996/49.6	119.9 (112.1,127.7)	100.0	625/26.2	150.8 (138.5,163.2)	100.0	222/16.5	81.2 (69.7,92.8)	100.0
	≥30	253/48.9	108.8 (92.2,125.4)	100.0	184/26.9	150.4 (125.0,175.9)	100.0	66/19.6	64.5 (42.4,86.6)	100.0
Recurrence	<30	713/0.0	90.3 (83.7,97.0)	75.3	457/0.0	115.1 (104.6,125.7)	76.3	155/0.0	61.3 (51.6,70.9)	75.4
	≥30	63/0.0	33.6 (25.3,41.9)	30.9	51/0.0	48.8 (35.4,62.2)	32.5	12/0.0	16.7 (7.2,26.1)	25.9
SPN	<30	96/8.5	11.1 (8.7,13.5)	9.2	66/4.5	15.5 (11.5,19.5)	10.3	16/2.9	5.2 (2.1,8.3)	6.4
	≥30	53/18.3	18.5 (10.9,26.1)	17.0	43/9.8	31.8 (19.5,44.1)	21.2	9/7.6	1.9 (-6.3,10.1)	3.0
Circulatory§	<30	37/4.9	4.1 (2.6,5.6)	3.4	24/2.7	5.4 (3.0,7.8)	3.6	7/1.7	2.1 (0.0,4.1)	2.6
	≥30	44/12.5	16.8 (9.9,23.7)	15.4	30/7.0	22.0 (11.8,32.3)	14.6	13/5.0	11.2 (1.3,21.0)	17.3
Cardiac	<30	10/3.2	0.9 (0.1,1.6)	0.7	2/1.7	0.1 (-0.6,0.8)	0.0	3/1.1	0.8 (-0.6,2.1)	0.9
	≥30	18/9.3	4.6 (0.2,9.0)	4.2	8/5.3	2.6 (-2.7,7.9)	1.7	9/3.7	7.4 (-0.8,15.6)	11.5
Stroke	<30	19/1.3	2.2 (1.2,3.3)	1.9	16/0.7	3.9 (1.9,5.8)	2.6	3/0.4	1.0 (-0.3,2.4)	1.2
	≥30	20/2.2	9.5 (4.8,14.2)	8.7	19/1.2	17.1 (8.9,25.2)	11.3	1/0.9	0.2 (-2.6,2.9)	0.2
Respiratory	<30	41/2.1	4.9 (3.3,6.5)	4.1	21/1.1	5.0 (2.7,7.3)	3.3	13/0.7	4.9 (2.1,7.7)	6.0
	≥30	29/2.9	13.9 (8.3,19.5)	12.8	21/1.6	18.6 (10.0,27.2)	12.4	7/1.2	8.1 (0.8,15.3)	12.5
External	<30	40/22.8	2.2 (0.6,3.8)	1.8	21/12.1	2.2 (-0.0,4.5)	1.5	12/7.4	1.8 (-0.9,4.5)	2.2
	≥30	18/5.5	6.7 (2.2,11.1)	6.1	10/3.2	6.5 (0.6,12.5)	4.3	8/2.0	8.3 (0.6,16.0)	12.9
OtherΔ	<30	69/11.4	7.3 (5.2,9.4)	6.1	36/5.9	7.6 (4.6,10.6)	5.0	19/3.8	6.0 (2.6,9.4)	7.4
	≥30	46/9.7	19.4 (12.3,26.4)	17.8	29/5.4	22.6 (12.5,32.7)	15.0	17/3.8	18.4 (7.2,29.6)	28.5

AER: absolute excess risks, CNS: central nervous system, CI: confidence interval, O/E: observed/ expected, RT: radiotherapy, SPN: subsequent primary neoplasm

Δ comprises deaths due to blood, infection, endocrine, mental, nervous system disease, digestive, musculoskeletal, genitourinary, perinatal and other

§ category consists of cardiac, stroke and other cardiovascular conditions; the latter conditions have not been reported

Table 3.4 Cause of death specific absolute excess risks for CNS tumour subtype

Cause of death	Years from diagnosis	Craniopharyngioma			Medulloblastoma			Astrocytoma		
		O/E	AER (95%CI)	%	O/E	AER (95%CI)	%	O/E	AER (95%CI)	%
All causes	<30	117/4.2	181.8 (147.6,216.0)	100.0	200/6.6	180.1 (154.3,206.0)	100.0	436/25.4	98.2(88.4,108.0)	100.0
	≥30	32/3.4	226.9 (138.9,314.9)	100.0	39/4.5	168.6 (108.7,228.4)	100.0	117/27.5	86.8(66.3,107.4)	100.0
Recurrence	<30	78/0.0	125.7 (97.8,153.6)	69.1	145/0.0	135.1 (113.1,157.1)	75.0	305/0.0	73.0 (64.8,81.2)	74.3
	≥30	8/0.0	63.5 (19.5,107.5)	28.0	7/0.0	34.2 (8.9,59.6)	20.3	31/0.0	30.1 (19.5,40.7)	34.6
SPN	<30	2/0.7	2.1 (-2.4,6.6)	1.2	31/1.0	28.0 (17.8,38.1)	15.5	45/4.5	9.7 (6.6,12.8)	9.9
	≥30	1/1.2	-1.7 (-17.3,13.9)	-0.7	18/1.5	80.7 (40.0,121.3)	47.9	22/10.6	11.0 (2.1,20.0)	12.7
Circulatory[§]	<30	10/0.4	15.4 (5.4,25.4)	8.5	6/0.6	5.0 (0.6,9.5)	2.8	17/2.5	3.5 (1.5,5.4)	3.5
	≥30	11/0.9	80.2 (28.6,131.8)	35.3	6/1.1	23.8 (0.3,47.3)	14.1	15/7.0	7.8 (0.4,15.1)	9.0
Cardiac	<30	3/0.3	4.4 (-1.1,9.9)	2.4	1/0.4	0.6 (-1.3,2.4)	0.3	6/1.6	1.0 (-0.1,2.2)	1.1
	≥30	3/0.7	18.4 (-8.5,45.3)	8.1	3/0.9	10.5 (-6.1,27.1)	6.2	8/5.2	2.7 (-2.6,8.1)	3.2
Stroke	<30	5/0.1	7.9 (0.8,15.0)	4.3	3/0.1	2.7 (-0.5,5.8)	1.5	9/0.7	2.0 (0.6,3.4)	2.0
	≥30	4/0.1	30.6 (-0.5,61.7)	13.5	3/0.2	13.7 (-2.9,30.3)	8.2	7/1.2	5.6 (0.6,10.6)	6.4
Respiratory	<30	11/0.2	17.4 (7.0,27.9)	9.6	8/0.3	7.2 (2.0,12.4)	4.0	14/1.1	3.1 (1.3,4.8)	3.1
	≥30	3/0.2	22.3 (-4.7,49.2)	9.8	4/0.2	18.4 (-0.8,37.6)	10.9	13/1.7	11.0 (4.1,17.8)	12.7
External	<30	3/2.0	1.7 (-3.8,7.2)	0.9	2/3.2	-1.2 (-3.7,1.4)	-0.6	21/11.5	2.3 (0.1,4.4)	2.3
	≥30	1/0.4	4.7 (-10.8,20.3)	2.1	3/0.7	11.4 (-5.2,28.0)	6.8	10/2.9	6.9 (0.9,12.9)	7.9
Other[Δ]	<30	13/0.9	19.4 (8.0,30.8)	10.7	8/1.5	6.0 (0.9,11.2)	3.3	34/5.9	6.7 (4.0,9.5)	6.9
	≥30	8/0.7	57.9 (13.9,101.9)	25.5	1/1.0	0.1 (-9.5,9.7)	0.0	26/5.3	20.1 (10.4,29.8)	23.1

AER: absolute excess risks, CNS: central nervous system, CI: confidence interval, O/E: observed/ expected, SPN: subsequent primary neoplasm

Δ comprises deaths due to blood, infection, endocrine, mental, nervous system disease, digestive, musculoskeletal, genitourinary, perinatal and other

§ category consists of cardiac, stroke and other cardiovascular conditions; the latter conditions have not been reported

Figure 3.1 Cumulative mortality for causes of death among all childhood cancer survivors diagnosed with a CNS neoplasm overall and more specifically by CNS subtypes of astrocytoma, craniopharyngioma and medulloblastoma

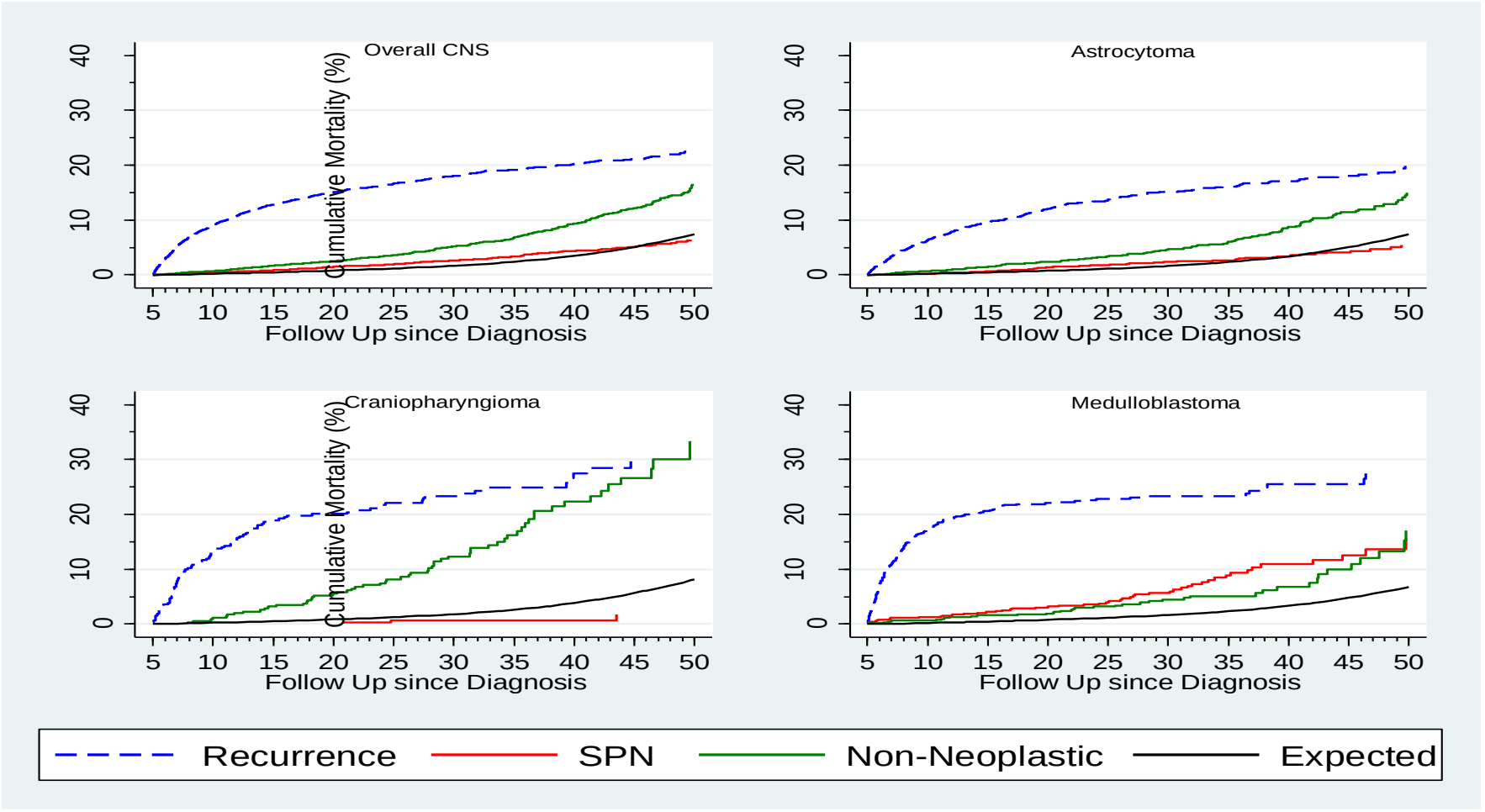


Table 3.5 Overall and site specific Standardised Incidence Ratios and Absolute Excess Risks for Subsequent Primary Neoplasms developing in CNS tumour survivors

	SPN	Obs/Exp	SIR (95% CI)†	AER (95% CI)‡
All CNS†	Any Cancer Site	165/60.1	2.7 (2.4-3.2)	12.2 (9.3-15.1)
Survivors	Glioma	50/2.3	21.8 (16.6-28.8)	5.5 (4.1-7.4)
	Digestive	25/6.9	3.6 (2.5-5.4)	2.1 (1.0-3.2)
	Genitourinary	23/14.3	1.6 (1.1-2.4)	1.0 (-0.1-2.1)
	Thyroid	11/1.2	9.5 (5.2-17.1)	1.1 (0.4 -1.9)
	Breast	10/13.1	0.8 (0.4-1.4)	0 (-1.1-0.4)
Cranial RT – No	Glioma	7/0.74	9.5 (4.5-19.7)	2.4 (0.4-4.3)
Cranial RT – Yes	Glioma	41/1.2	33.6 (24.7-45.6)	8.8 (6.0-11.6)
Craniopharyngioma	Any Cancer Site	3/4.3	0.7 (0.2-2.1)	0 (-7.2-3.1)
Medulloblastoma§	Any Cancer Site	50/5.9	8.4 (6.4-11.1)	39.3 (27.0-51.7)
	Glioma	12/0.3	43.4 (24.6-76.4)	10.5 (4.45-16.5)
Astrocytoma	Any Cancer Site	78/33.7	2.3 (1.9-2.9)	9.7 (5.9-13.4)
	Glioma	22/1.2	18.0 (11.9-27.4)	4.5 (2.5-6.5)

AER: absolute excess risk, CNS: central nervous system, CI: confidence interval, Obs/Exp: observed/expected, RT: radiotherapy, SIR: standardised incidence ratio

† Other SPNs include: 8 connective & soft tissue, 7 Leukaemia, 6 respiratory, 6 bone & articular cartilage, 5 oral cavity & pharynx, 5 melanoma skin cancer, 2 Hodgkin Lymphoma, 2 Non-Hodgkin Lymphoma, 2 other endocrine, 1 other lymphoid, 1 eye and 1 others

§ SPNs include: 12 CNS, 12 digestive and peritoneum, 6 female genital organs, 6 thyroid, 4 leukaemia, 2 breast, 2 oral cavity & pharynx, 2 bone & articular cartilage, 1 respiratory & intrathoracic, 1 melanoma skin cancer, 1 male genital organs, 1 eye

‡AER is shown per 10,000 person years

Figure 3.2 Observed Cumulative Incidence of Subsequent Primary Neoplasms among all CNS childhood cancer survivors, cumulative incidence of specific CNS subsequent primary neoplasms and cumulative incidence of SPNs after an astrocytoma and medulloblastoma respectively.

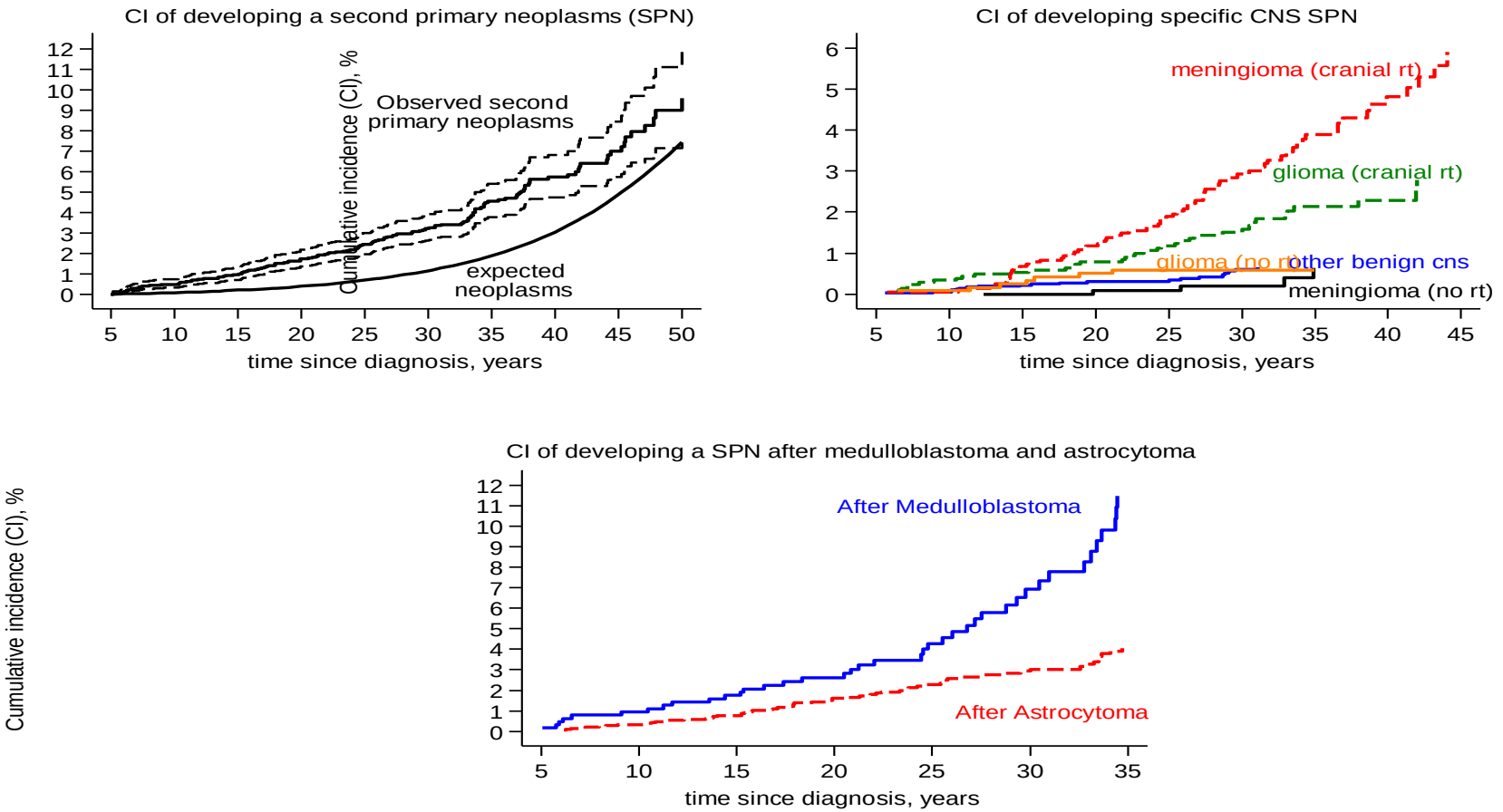


Table 3.6 Odds ratios of the different health and social outcomes for all survivors of a CNS tumour combined, for survivors treated with cranial radiotherapy and for survivors of specific types of CNS tumours relative to the general population

Outcome	CNS overall	CNS overall Cranial RT yes	CNS overall Cranial RT no	Craniopharyn-gioma	Medullo-blastoma	Astrocy-toma
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Education[a]						
University degree	0.4 (0.3-0.5)	0.3 (0.2-0.4)	0.6 (0.5-0.7)	0.4 (0.2-0.7)	0.3 (0.2-0.4)	0.5 (0.4-0.6)
Teaching qualification	0.5 (0.5-0.6)	0.5 (0.4-0.6)	0.6 (0.5-0.8)	0.5 (0.4-0.8)	0.3 (0.2-0.5)	0.6 (0.5-0.7)
A levels or higher	0.5 (0.5-0.6)	0.5 (0.4-0.5)	0.7 (0.6-0.8)	0.8 (0.6-1.9)	0.3 (0.2-0.4)	0.5 (0.5-0.6)
O levels or higher	0.5 (0.4-0.5)	0.4 (0.6-0.5)	0.7 (0.6-0.9)	0.9 (0.6-1.4)	0.4 (0.2-0.3)	0.5 (0.4-0.7)
Smoking[b]						
Current regular smoker	0.3 (0.3-0.4)	0.3 (0.2-0.3)	0.5 (0.4-0.7)	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.4 (0.3-0.5)
Alcohol consumption[b]						
Current drinker	0.3 (0.3-0.4)	0.3 (0.3-0.4)	0.5 (0.4-0.6)	0.2 (0.1-0.2)	0.3 (0.2-0.4)	0.4 (0.3-0.5)
Consuming over recommendation	0.5 (0.4-0.6)	0.4 (0.3-0.5)	0.8 (0.6-1.0)	0.4 (0.2-0.8)	0.2 (0.1-0.4)	0.6 (0.5-0.7)
Consuming harmful amounts	0.3 (0.2-0.5)	0.3 (0.2-0.5)	0.4 (0.2-0.6)	0.4 (0.1-1.4)	0.3 (0.1-0.7)	0.4 (0.3-0.6)
Marriage[c]						
Males	0.2 (0.2-0.3)	0.2 (0.1-0.2)	0.3 (0.3-0.4)	0.2 (0.2-0.4)	0.1 (0.1-0.2)	0.3 (0.2-0.3)
Females	0.3 (0.3-0.4)	0.2 (0.2-0.3)	0.5 (0.4-0.7)	0.2 (0.1-0.3)	0.2 (0.1-0.4)	0.4 (0.3-0.4)
Health care utilisation[d]						
Talked to a doctor	1.2 (1.1-1.4)	1.1 (0.9-1.3)	1.3 (1.1-1.6)	2.2 (1.5-3.1)	1.2 (0.9-1.7)	1.1 (0.9-1.3)
Attended hospital outpatient	3.1 (2.7-3.5)	3.1 (2.6-3.6)	2.6 (2.1-3.1)	7.0 (5.0-9.7)	3.1 (2.4-4.1)	2.7 (2.3-3.1)
Hospitalised as a day patient	1.6 (1.3-1.8)	1.4 (1.2-1.8)	1.4 (1.1-1.9)	3.1 (2.1-4.5)	1.6 (1.1-2.3)	1.4 (1.2-1.8)
Hospitalised as an inpatient	2.4 (2.1-2.8)	2.4 (1.9-3.0)	2.1 (1.6-2.8)	3.6 (2.4-5.6)	2.9 (2.0-4.1)	2.1 (1.7-2.6)
BMI[e]						
Male	1.6 (1.3-2.1)	1.8 (1.4-2.4)	1.3 (0.9-1.7)	3.9 (2.2-7.0)	1.3 (0.9-1.9)	1.5 (1.2-2.0)
Female	2.4 (1.9-3.1)	3.5 (2.6-4.7)	1.7 (1.3-2.3)	11.9 (5.7-24.6)	3.1 (1.9-5.2)	2.4 (1.8-3.1)

BMI: body mass index, CNS: central nervous system, CI confidence interval, OR: odds ratio, RT: radiotherapy

[a] From a generalised estimating equation logistic regression model, taking into account the General Household Survey weighting factor, controlling for age and sex. Population data from the General Household Survey (2002) was used for the reference group

[b] From a generalised estimating equation logistic regression model controlling for age at questionnaire completion (≤69 years), gender, legal marital status, socioeconomic classification, educational attainment and region. The model took into account the General Household Survey (GHS) weighting factor and the GHS data (2002) was used as the reference group

[c] Calculated using Mantel Haenszel Odds Ratio, adjusting for age and sex

[d] From a generalised estimating equation logistic regression model, taking into account the General Household Survey weighting factor, controlling for age at questionnaire completion, gender and educational attainment. Outcomes reported were survivors doing these at least once vs never as compared to the general population

[e] Logistic models were adjusted for age and socio-economic status

Table 3.7 Differences in mean scores for eight SF-36 scales between CNS childhood cancer survivors and UK norms

SF36 Scale	*CNS overall*	*CNS overall Cranial RT yes*	*CNS overall Cranial RT no*	*Craniopharyngioma*	*Medulloblastoma*	*Astrocytoma*
	difference (95%CI)*	*difference* (95%CI)*	*difference* (95%CI)*	*difference* (95%CI)*	*difference* (95%CI)*	*difference* (95%CI)*
Physical Function	-15.7 (-16.7 to -14.7)	-19.8 (-21.1 to -18.4)	-10.7 (-12.2 to -9.1)	-16.3 (-19.4 to -13.2)	-19.3 (-21.7 to -16.9)	-13.9 (-15.2 to -12.7)
Role-Physical	-14.7 (-16.3 to -13.2)	-17.9 (-20.0 to -15.7)	-10.0 (-12.4 to -7.5)	-19.6 (-24.5 to -14.7)	-18.3 (-22.0 to -14.6)	-12.4 (-14.4 to -10.5)
Role-Emotional	-5.5 (-7.1 to -3.9)	-6.9 (-9.1 to -4.7)	-4.4 (-6.9 to -1.9)	-5.4 (-10.5 to -0.3)	-6.1 (-9.9 to -2.2	-4.1 (-6.2 to -2.1)
Social Functioning	-11.6 (-12.6 to - 10.5)	-13.5 (-14.9 to -12.1)	-9.5 (-11.1 to -7.8)	-13.3 (-16.5 to -10.0)	-12.5 (-15.0 to -10.0)	-10.1 (-11.5 to - 8.8)
Mental Health	-4.4 (-5.3 to -3.6)	-4.5 (-5.7 to -3.3)	-4.4 (-5.8 to -3.1)	-4.2 (-6.9 to -1.5)	-2.6 (-4.7 to -0.6)	-4.4 (-5.4 to -3.3)
Vitality	-5.5 (-6.5 to - 4.5)	-6.8 (-8.2 to -5.5)	-3.7 (-5.3 to -2.2)	-11.4 (-14.5 to -8.3)	-3.9 (-6.2 to -1.5)	-4.8 (-6.0 to -3.5)
Pain	-3.4 (-4.4 to -2.3)	-3.5 (-5.0 to -2.0)	-3.8 (-5.5 to -2.1)	-7.1 (-10.5 to -3.7)	-2.0 (-4.6 to -0.6)	-3.0 (-4.3 to -1.6)
General Health Perception	-10.7 (-11.7 to - 9.6)	-12.6 (-14.0 to -11.3)	-8.4 (-10.0 to -6.8)	-22.1 (-25.3 to -18.9)	-10.2 (-12.7 to -7.8)	-9.1 (-10.4 to -7.8)

BCCSS: British Childhood Cancer Survivor Study, CNS: Central Nervous System, CI: confidence interval, RT: radiotherapy, SF-36:short form health-status survey

*Linear regression coefficient adjusted for sex and age at questionnaire completion

Table 3.8 Directly standardised percentage experiencing specific outcome within the SF-36 for CNS subgroups as compared to the UK normal population

SF-36 Scale	Individual item	UK norms (%)	CNS overall (%)§	CNS overall Cranial RT yes (%)§	CNS overall RT no (%)§	Craniopharyngioma (%)§	Medulloblastoma (%)§	Astrocytoma (%)§
Physical function†	Vigorous activities	54	68	73	60	83	78	64
	Moderate activities*	8	38	46	31	45	48	34
	Lifting or carrying groceries	22	38	44	31	40	43	34
	Climbing several flights of stairs	20	44	52	36	53	59	40
	Climbing one flight of stairs	5	28	35	21	23	44	24
	Bending, kneeling or stooping	15	41	46	34	38	45	39
	Walking more than one mile	11	42	49	34	54	53	36
	Walking half a mile	6	30	37	24	31	41	26
	Walking 100 yards	3	23	29	17	19	27	19
	Bathing and dressing yourself	3	22	27	15	24	20	18
Role Limitation-Physical†	Cut down the amount of time spent on work/other activities	11	24	28	20	27	28	21
	Accomplished less than you would like	18	34	39	28	41	42	30
	Were limited in the kind of work/other activities	13	35	40	28	45	46	30
	Had difficulty performing work/other activities	16	34	39	28	43	42	29
Social Functioning†	What extent have your physical or emotional problems interfered with your normal social activities with family, friends, neighbours or groups	7	17	20	14	17	16	15
	How much time in the last month has your health limited social activities	6	24	25	17	23	21	19
General health perception	% who say their health is 'poor' or 'fair'	12	28	31	25	43	31	23
	I seem to get ill more easily than other people Δ	6	18	20	17	41	16	15
	I am as healthy as anybody i know Δ	88	72	33	22	51	75	75
	I expect my health to get worse Δ	13	15	17	16	21	8	15
	My health is excellent Δ	83	67	38	29	48	69	70

CNS: Central Nervous System, RT: radiotherapy SF-36: Short Form Health Status Survey, UK: United Kingdom

†For these individual questionnaire items, the percentage is reported as percent limited

Δ For these individual items, the percentage is reported as percent mostly/definitely agree

§ Directly standardised for age and sex

* Moving a table, pushing a vacuum, bowling or playing golf

CHAPTER 4 CEREBROVASCULAR DISEASE AMONG FIVE-YEAR SURVIVORS OF CHILDHOOD CANCER USING HOSPITAL EPISODE STATISTICS: THE BRITISH CHILDHOOD CANCER SURVIVOR STUDY

4.1 ABSTRACT

Background: Survivors of childhood cancer are at increased risk of hospitalisation due to cerebrovascular disease; however, the extent to which long-term childhood cancer survivors have been hospitalised for specific cerebrovascular conditions, including cerebral haemorrhage and ischaemic strokes, remains largely unknown.

Methods: The population-based British Childhood Cancer Survivor Study (BCCSS) cohort, comprising 34,489 individuals diagnosed with cancer aged <15 years, between 1940 and 2006, in Britain and who survived at least five years, was linked to the inpatient Hospital Episode Statistics (HES) database for England. The excess risk of hospitalisation due to specific cerebrovascular conditions were quantified by standardised hospitalisation ratios (SHR) (defined as Observed/Expected) and absolute excess risks (AER) per 10,000 person-years. Potential explanatory factors for cerebrovascular hospitalisation were investigated using multivariable Poisson regression.

Results: Overall, 299 survivors were hospitalised for a cerebrovascular condition compared to 59 expected (SHR=5.1, 95%CI:4.5-5.7) with survivors of a central nervous system (CNS) tumour (SHR=11.9, 95%CI:10.3-13.7, AER=8.5, 95%CI:3.9-18.3) and leukaemia (SHR=5.6, 95%CI:4.2-7.4, AER=2.3, 95%CI:1.0-5.0) at the greatest excess risk. Of the specific cerebrovascular conditions, the greatest observed hospitalisations among survivors were for cerebral haemorrhage (SHR=8.1, 95%CI:6.7-9.8) and ischaemic stroke (SHR=5.2, 95%CI:4.3-6.2), with CNS tumour survivors at particular increased risk. Previous treatment with cranial irradiation was associated with increased risk of being hospitalised for a cerebrovascular condition over that expected (SHR=15.6, 95%CI:13.0-18.9). In absolute terms this equated to 58 additional hospitalisations per 10,000 person-years.

Conclusion: CNS tumours and leukaemia are at the greatest risk of cerebrovascular hospitalisations and more specifically hospitalisations due to cerebral haemorrhage and

ischaemic stroke. Cranial irradiation is a strong risk factor associated with survivors being hospitalised for cerebrovascular complications. A risk-stratified approach to clinical follow-up, would ensure survivors at highest risk of cerebrovascular complications undergo surveillance.

4.2 INTRODUCTION

Survival after childhood cancer has dramatically improved over the last few decades with overall five-year survival in the UK now exceeding 80% (220). The number of long-term survivors continues to increase due to improvements in treatment but many sub-groups of survivors are at an increased risk of developing adverse health outcomes many years after treatment (47, 50). In a study by the CCSS, almost 30% of childhood cancer survivors had a severe or life-threatening chronic condition by a mean age of 26.6 years, with CNS tumour survivors being some of the highest at risk (47).

As a result of the increased risk of adverse health outcomes, survivors are more likely to be hospitalised compared to their siblings and the general population (122, 123, 221). Previous studies have reported the excess risks of hospitalisation due to overall circulatory conditions with risks estimated up to 9-fold that expected (122, 124, 222).

However, the estimated excess risks of hospitalisation among childhood cancer survivors *specifically* due to cerebrovascular disease as reported from large scale population-based studies remains largely unknown. The exception is a recent study from Scandinavia (Adult Life after Childhood Cancer in Scandinavia (ALiCCS)) using 32,308 one-year childhood cancer survivors diagnosed between 1943 and 2008 (71). They reported a 4-fold increased risk among survivors being hospitalised due to cerebrovascular disease compared to expected (71).

The aims of this study were to: determine the risks of hospitalisations due to a cerebrovascular condition among five-year survivors of childhood cancer as compared to that expected from the general population through electronic record linkage of the British Childhood Cancer Survivor Study (BCCSS) with the national Hospital Episode Statistics (HES) database; investigate the risk of specific types of cerebrovascular conditions (cerebral haemorrhage and

ischaemic stroke) in the survivors; examine any variation in these risks by cancer type and cranial irradiation.

To our knowledge, this is the only second large scale population-based study that has investigated the risk of hospitalisations explicitly due to cerebrovascular conditions among childhood cancer survivors. In addition this study had access to whether individuals received direct cranial irradiation which the Scandinavian study did not have. Survivors of childhood cancer previously treated with cranial irradiation have been shown to be at increased risk of developing cerebrovascular disease (182) with the risk showing a linear dose response relationship with radiation dose delivered to the brain (110, 111).

4.3 METHODS

4.3.1 British Childhood Cancer Survivor Study

The British Childhood Cancer Survivor Study is a population-based cohort of 34,489 individuals diagnosed with a childhood cancer between 1940 and 2006 inclusive, before age 15 years, in Great Britain and who survived for at least five years from diagnosis. Individuals in the cohort were identified using the population-based National Registry of Childhood Tumours. Ethical approval for the study was obtained from the National Research Ethics Committee (10/H1102/86) and legal approval from the Health Research Authority's Confidentiality Advisory Group (Section 251) (ECC 2-02 (f)/2011).

4.3.2 Hospital Episode Statistics

Hospital Episode Statistics (HES) is a centralised database which contains records from 1st April 1997 of all inpatient admissions to National Health Service (NHS) hospitals within England (223). HES data was provided by the Health and Social Care Information Centre (HSCIC). Records in the HES database are classified into hospital episodes; each of these hospital episodes relates to a period of care for a patient under a single consultant. The

information contained within a HES record includes an episode start date, an episode end date, a primary diagnosis code and additional subsidiary diagnosis codes, which may relate to pre-existing conditions or other conditions diagnosed during hospital admission, but there are no dates associated with these subsidiary conditions. The primary diagnosis which accounts for hospital admission is classified using the International Classification of Diseases 10th revision (ICD-10) (224).

The BCCSS cohort was electronically linked to the inpatient HES database for England for the period from the 1st April 1997 to 31st December 2012 using NHS number, date of birth and gender. Childhood cancer survivors that were Scottish or Welsh residents were excluded as were those who had died before April 1st 1997. Thus the total number of survivors excluded from the overall cohort was 6,650.

4.3.3 Definition of cerebrovascular events

To identify a cerebrovascular hospitalisation (ICD-10: I60-69), the primary diagnosis code for each HES record was used. The following ICD-10 codes were used to classify hospitalisations for specific cerebrovascular conditions: subarachnoid haemorrhage (I60), cerebral haemorrhage (I61-I62), ischaemic stroke (I63), unspecified stroke (I64) and other cerebrovascular disease (I65-I69). The episode start date was used to determine occurrence of a first hospitalisation since this corresponds with the primary diagnosis code. For overall cerebrovascular hospitalisations, the first occurrence of any cerebrovascular hospitalisation per individual was taken. For cerebrovascular subtypes, the first occurrence of the cerebrovascular hospitalisation of interest per individual was taken. Only the first occurrence of a hospitalisation was ascertained so the same condition was not recorded multiple times.

4.3.4 Statistical methods

Any cerebrovascular hospitalisations that occurred before five-year survival in individuals were excluded from the analysis since we were only concerned with hospitalisations occurring at five-year survival or beyond. Survivors entered the period of risk at the latest of: date of five-year survival or 1st April 1997. Survivors exited the study at the earliest of: date of death, date of loss-to follow-up, date of hospitalisation for a cerebrovascular condition (i.e. event date) or 31st December 2012 (study end date).

Standardised hospitalisation ratios (SHR) and absolute excess risks (AER) were calculated for hospitalisation due to any cerebrovascular condition and for specific types of cerebrovascular conditions. The SHR was defined as the number of observed cerebrovascular hospitalisations divided by the number of expected cerebrovascular hospitalisations. The AER was defined as the number of observed cerebrovascular hospitalisations minus the number of expected cerebrovascular hospitalisations divided by the number of person-years at risk multiplied by 10,000. The AER may be interpreted as the number of additional hospitalisations for each year of follow-up per 10,000 survivors attributable to the original childhood cancer diagnosis or its treatment.

To derive the expected number of cerebrovascular hospitalisations, the number of individuals with a cerebrovascular hospitalisation in the entire HES dataset for England (N=27,839) was calculated for each sex, single year of age and single calendar year stratum. These numbers of observed hospitalisations were divided by the relevant mid-year population count estimate for England corresponding to each sex, age and calendar year specific stratum from the Office of National Statistics (225).

A multivariable Poisson regression model with the log of the expected as the offset, was used to derive relative risks (RR) to determine the simultaneous effect of the following variables on

hospitalisation due to cerebrovascular events: gender, childhood cancer diagnosis, attained age (<20/20-29/30-39/40-49/ ≥50 years), age at diagnosis (0-4/5-9/10-14 years) and decade of diagnosis (<1970/1970-79/1980-89/1990-99/2000-06). A similar multivariable Poisson regression model with the log of the person-years as the offset and a special link function was fitted to derive excess hospitalisation ratios (EHRs). EHRs are essentially the ratios of AERs adjusted for the confounders which were fitted within the model. The effect of previous treatment with cranial irradiation on developing a cerebrovascular hospitalisation was investigated in survivors diagnosed with childhood cancer between 1940 and 1991 because treatment information was available for this period only. Statistical significance was taken at the 5% level (two sided tests). Analyses were carried out using Stata statistical software (version 13.1; Stata Corp., College Station, TX).

4.4 RESULTS

4.4.1 Cohort characteristics

Of the 34,489 childhood cancer survivors in the cohort, 27,839 (80.7%) were eligible to be linked with HES after excluding the Scottish and Welsh residents and those who died before the 1st April 1997. The total person-years of follow-up were 312,869 years. The mean and median follow-up times were 11.2 years and 13.7 years, respectively (range:0-15.8 years). Overall, 299 (1.1%) survivors had been hospitalised for a cerebrovascular condition. When cerebrovascular subtypes were investigated, 118 (34%) hospitalisations were observed for ischaemic stroke, 104 (30%) hospitalisations for cerebral haemorrhage, 58 (17%) hospitalisations for unspecified stroke, 47 (13%) hospitalisations for other cerebrovascular conditions and 21(6%) hospitalisations for subarachnoid haemorrhage.

4.4.2 Hospitalisation for any cerebrovascular condition (Table 4.1)

Overall, survivors had 5-fold the expected risk (SHR=5.1, 95%CI:4.5-5.7) of being hospitalised for any cerebrovascular condition; this corresponded to an excess of 8 (AER=7.7, 95%CI:6.9-8.5) hospitalisations per 10,000 person-years. Survivors of CNS tumours (SHR=11.9, 95%CI:10.3-13.7) and leukaemia (SHR=5.6, 95%CI:4.2-7.4) were at the greatest risk of being hospitalised for a cerebrovascular condition. CNS tumour survivors and leukaemia survivors had an excess of 25 and 4 hospitalisations per 10,000 person-years respectively. Survivors of soft tissue sarcoma (SHR=2.8, 95%CI:1.7-4.8), neuroblastoma (SHR=2.5, 95%CI:1.1-6.1) and Hodgkin's disease (SHR=2.2, 95%CI:1.2-3.8) were also at increased risk of being hospitalised for a cerebrovascular condition. The SHR of being hospitalised due to any cerebrovascular type declined with increasing attained age (adjusted $P_{trend}<0.01$). In contrast the AER increased with increasing attained age (adjusted $P_{trend}=0.01$) with the number of additional hospitalisations increasing from 4 (per 10,000 per year) among those aged <20 years to 25 among those aged ≥50 years, respectively.

4.4.3 Hospitalisations due to cerebral haemorrhage (Table 4.2)

Survivors had 8-fold the expected risk, (SHR=8.1, 95%CI:6.7-9.8) of being hospitalised due to a cerebral haemorrhage, corresponding to an excess of 3 (AER=2.9, 95%CI:2.5-3.4) hospitalisations per 10,000 person-years. Female survivors had a 1.7-fold risk of cerebral haemorrhage relative to males, but both female and male survivors experienced 3 excess hospitalisations per 10,000 person-years. CNS tumour survivors (SHR=18.6, 95%CI:14.5-23.8, AER=8.5, 95%CI:6.5-11.1) and leukaemia (SHR=10.7, 95%CI:7.2-15.9, AER=2.4, 95%CI:1.5-3.7) survivors had the greatest excess risk in both relative and absolute terms of being hospitalised due to a cerebral haemorrhage. The SHR was greatest among those diagnosed in more recent decades (adjusted $P_{trend}=0.01$), survivors diagnosed in the 2000's

were at 7-fold the relative risk of cerebral haemorrhage compared with those diagnosed before 1970 (RR=7.0, 95%CI:1.6-31.0).

4.4.4 Hospitalisations due to ischaemic stroke (Table 4.3)

Survivors had 5-fold the expected risk (SHR=5.2, 95%CI:4.3-6.2) of being hospitalised due to an ischaemic stroke; this corresponds to an excess of 3 (AER=3.0, 95%CI:2.6-3.6) hospitalisations per 10,000 person-years. CNS tumour, leukaemia, NHL and bone sarcoma survivors had a 12-fold, 6-fold, 3-fold and 3-fold expected risk respectively of being hospitalised due to ischaemic stroke, which equated to AER values of 10, 2, 2 and 2 respectively. The SHR declined with increasing attained age from 14.3 (95%CI:7.7-26.6) among those aged <20 years to 2.8 (95%CI:2.0-4.0) among those aged ≥ 50 years (adjusted P_{trend}=0.04). In contrast, the AER increased with increased attained age (adjusted P_{trend}<0.001) with the number of additional hospitalisations increasing from 1 (per 10,000 per year) among those aged <20 years to 12 among those aged ≥50 years, respectively. There was suggestive evidence that both the SHR and AER declined with increased age at diagnosis (adjusted P_{trend}=0.04 and adjusted P_{trend}=0.05).

4.4.5 Hospitalisations of any cerebrovascular event among CNS tumour survivors (Table 4.4)

Among the CNS tumour survivors, the SHR declined with increased attained age (adjusted P_{trend}<0.001) from 51 in survivors aged <20 years to 6 among survivors aged ≥ 50 years.

4.4.6 Hospitalisations associated with treatment with cranial irradiation (Table 4.5)

In all childhood cancer survivors, cranial irradiation was associated with an excess risk of being hospitalised for a cerebrovascular condition of any type over that expected; in that those so treated there was a 12-fold increased risk over that expected (SHR=11.7, 95%CI:9.9-13.7) whereas survivors not treated with cranial irradiation had a 2-fold increased risk compared to

that expected (SHR=1.9,95%CI:1.5-2.5). In absolute terms this equated to 25 and 4 additional hospitalisations per 10,000 person-years, respectively.

Among CNS tumour survivors, cranial irradiation was associated with the risk of being hospitalised for a cerebrovascular condition in that those treated with cranial irradiation had a 16-fold increased risk compared to that expected (SHR=15.6,95%CI:13.0-18.9) with an excess of 58 hospitalisations (95%CI:48.0-70.8) per 10,000 person-years. For CNS tumour survivors not treated with cranial irradiation, the risk of being hospitalised for a cerebrovascular condition was 3-fold over that expected (SHR=3.0, 95%CI:1.9-4.9) with 9 additional hospitalisations per 10,000 person-years (AER=8.7, 95%CI:4.3-17.7). Within leukaemia survivors cranial irradiation was not significantly associated with either a relative or absolute increased risk of being hospitalised for a cerebrovascular condition over that expected. However, this could relate to insufficient statistical power as there is suggestive evidence of an increased risk associated with cranial prophylaxis in leukaemia survivors.

4.5 DISCUSSION

4.5.1 Main findings

In this large scale population-based study we found that survivors of childhood cancer are at a 5-fold expected risk of being hospitalised for a cerebrovascular condition. With respect to specific cerebrovascular conditions, survivors of childhood cancer are at an 8-fold expected risk of cerebral haemorrhage and a 5-fold expected risk of ischaemic stroke. Survivors of CNS tumours previously treated with cranial irradiation experienced a 16-fold expected risk for cerebrovascular disease; also CNS tumour survivors not treated with cranial irradiation experienced a 3-fold expected risk.

The 5-fold expected risk of a hospitalisation due to any cerebrovascular condition that we observed was similar to the 4-fold excess risk reported in the ALiCCS study, the only other

large scale population-based study investigating cerebrovascular hospitalisations (71). In the North American Childhood Cancer Survivor Study (CCSS), among 4,828 five-year leukaemia survivors, the relative risk of such survivors developing a late-occurring stroke was 6.4 (95%CI:3.0-13.8) compared to siblings which is consistent with our study (111). The overall risk of cerebrovascular disease among 1,367 five-year survivors of childhood cancer diagnosed between 0 and 14 years in a English regional study was higher (HRR=7.9) than that observed in our study (226). The period of diagnosis in this English regional study however ranged from 1991 to 2006 thus in comparison with our study they have a predominantly younger cohort, which could be a possible explanation in the difference of overall risk.

In our study, the SHR for any cerebrovascular condition declined with increasing attained age while the AER increased; similar trends were observed in the ALiCCS study (71). A reduction in SHR with increasing attained age among survivors is likely to be due to the increasing background risk of cerebrovascular disease in older individuals in the general population. An increasing AER implies that an additional number of survivors were hospitalised, compared with expected, which increased with attained age and again this relates to the background risk increasing with age in the general population.

4.5.2 Hospitalisations due to cerebral haemorrhage and ischaemic stroke

Survivors of all childhood cancer in our study had an 8-fold expected risk of being hospitalised for a cerebral haemorrhage and a 5-fold expected risk of being hospitalised for an ischaemic stroke. These findings are similar to the reported 8-fold excess risk of being hospitalised due to cerebral haemorrhage and the 4-fold excess risk for ischaemic stroke among all childhood cancer survivors in the ALiCCS study (71). In our study, the declining SHR with increased attained age with respect to survivors being hospitalised for ischaemic stroke is likely to be due to the increasing risk of stroke with age in the general population.

For cerebral haemorrhage hospitalisations, the risk of hospitalisation increased with decade of diagnosis thus more recently diagnosed survivors appear to be at higher risk; this may be due to survival bias between survivors diagnosed decades ago compared with those in recent decades. Survivors diagnosed decades ago are more likely to have died before developing the adverse outcome of cerebral haemorrhage compared with survivors diagnosed more recently.

4.5.3 CNS tumour survivors and treatment with cranial irradiation

CNS tumour survivors in our study were at the greatest risk of any cerebrovascular condition, specifically cerebral haemorrhage and ischaemic stroke. High risks of hospitalisation due to cerebrovascular disease after a CNS tumour were also reported in the ALiCCS study (71). In particular, a very high risk of hospitalisation due to cerebral haemorrhage after a CNS tumour was reported in the ALiCCS study, 18-fold that expected which was similar to the 19-fold risk found in our study (71). The relative risk of brain tumour survivors developing a stroke compared to siblings in a CCSS study was reported to be 29.0 (95%CI:13.8-60.7) (111), which is higher than what we report in our study but the confidence intervals for the CCSS are wide and our risk estimate of 18.6 (95%CI:14.5-23.8) for cerebral haemorrhage after CNS tumours falls within their confidence bounds. As the CCSS is based in North America survivors could have been treated more aggressively with cranial irradiation than in our British study; over 50% of CNS tumour survivors in the CCSS study were treated with radiation doses of ≥30Gy. The risk of stroke among CNS tumour survivors treated without cranial irradiation in the CCSS study is similar to the risk of cerebrovascular disease we report for all CNS tumour survivors in our study.

AERs increased substantially with increased attained age among CNS tumour survivors thus the absolute number of CNS survivors being hospitalised are in substantial excess to that expected, particularly with older survivors.

We were also in the position to investigate the risk of hospitalisation associated with cranial irradiation among CNS tumour survivors which the ALiCCS study could not do. We found survivors of CNS tumours previously treated with cranial irradiation to be at increased risk of hospitalisations due to cerebrovascular disease. In the CCSS, survivors of childhood cancer previously treated with cranial irradiation have been reported to be at an increased risk of developing cerebrovascular disease, notably CNS tumour survivors (110, 111). However, CNS tumour survivors who did not receive cranial irradiation in our study still had an increased risk of being hospitalised for a cerebrovascular condition compared to that expected, suggesting previous treatment with surgery may confer increased risk of cerebrovascular disease. The CCSS also found an elevated risk for both CNS tumour survivors who had not been treated with cranial irradiation in their risk of stroke compared with siblings, although the risks reported were higher than in our study (111).

4.5.4 Biological mechanisms

The biological mechanisms by which cranial irradiation may increase the risk of cerebrovascular disease in childhood cancer survivors are not clear. Potential mechanisms for radiation induced stroke may include the development of atherosclerosis through chronic inflammation in the intracranial vasculature, which can either lead to narrowing of the blood vessels or formation of blood clots (227-229). Metabolic syndrome is a late effect recognised in childhood cancer survivors which encompasses conditions of hypertension, hyperlipidaemia, obesity and type 2 diabetes (230, 231). Previous radiation vasculature damage combined with metabolic syndrome may influence the development of cerebrovascular disease (227, 232) .

4.5.5 Study Limitations

Potential limitations of our study include: (i) the lack of treatment information for those survivors diagnosed post 31st December 1991. However, our study did have available treatment exposure for survivors diagnosed between 1940 and 1991 which the ALiCCS study did not have. The comprehensive effect of treatment (i.e., dose response) is currently being investigated through case-control studies in the European funded CEREBRAD study, of which the BCCSS is a collaborative partner (233). (ii) We were not able to report risk estimates for known modifiable risk factors for stroke such as hypertension and diabetes mellitus. Lifestyle factors should also be considered in addition to treatment factors in the risk of cerebrovascular conditions as tobacco use, poor diet, inactivity and alcohol consumption, are known to increase the risk of stroke (234). (iii) The causes of hospitalisation in HES are not validated but there are advantages to using electronic record linkage to ascertain outcomes as opposed to self-reported data. For example, we do not have the issue of non-responder bias that arises in survivors self-completing questionnaires and by using two population-based sources, the numbers of survivors being lost-to-follow-up is likely to be less than non-population-based ascertainment. An advantage of our study is that we were able to address hospitalisations due to more specific diseases with electronic record linkage as such information is available in HES. For example, subtypes of cerebrovascular disease whereas broad categories are often used in self-reported questionnaires to ascertain outcomes (235). (iv) Since entry into HES is from 1997 there is the potential that some of our survivors may have had the event of interest before study enrolment, i.e. a hospitalisation due to a cerebrovascular condition but the date of such an event would be unknown thus our outcome estimates would be under-estimated. In the comparable ALiCCS study, the time of entry into the study from childhood cancer diagnosis and linkage with hospital registers has a substantially smaller time lag thus due to greater data completeness, left censoring requires

less consideration than in our study. However a sensitivity analysis was conducted with survivors diagnosed before 1997 and post 1997 in our study and there was no evidence of an interaction; between the effect of age at diagnosis and pre- and post-1997 achievement of 5-year survival on hospitalisation due to a cerebrovascular condition; between the effect of decade of diagnosis and pre-and post-1997 achievement of 5-year survival on hospitalisation due to a cerebrovascular condition (results not shown). Thus our overall results can be reported in confidence despite the issue of left censoring.

Current childhood cancer survivorship guidelines from the UK (CCLG and SIGN) do not include cerebrovascular complications as a potential late effect (17, 164). Irradiation ≥18Gy given in specified fields such as cranial, ear and nasopharyngeal regions are indicated for potential cerebrovascular complications among childhood cancer survivors in North America and annual neurological examinations are recommended among survivors who have received such treatment (121). The type of surveillance recommended to survivors in the UK requires further consideration but the evidence provided in this study should at least highlight survivor groups at greater risk of cerebrovascular late effects. It is difficult to monitor cerebrovascular late effects, one suggestion has been magnetic resonance imaging scans but these are costly investigations and the benefit gained from such a procedure in terms of stroke prevention for example, may be minimal. Patients may wish to consider preventative measures in terms of lifestyle factors which could increase their risk of developing cerebrovascular conditions, for example, stroke. Empowering survivors with such knowledge of preventative measures will enable them to take more control over their health, which could provide more long-term benefit. Preventative measures may include smoking cessation or a reduction in tobacco intake, dietary advice which advocates lower cholesterol and salt intake, regular exercise and

a reduction in alcohol consumption. Other preventative measures can involve medication for underlying conditions such as statins for hypercholesterolemia and angiotensin-converting enzyme (ACE) inhibitors for hypertension, two conditions which are considered risk factors for cerebrovascular disease.

4.5.6 Conclusions

Through the use of electronic record linkage, we have been able to provide empirical evidence that childhood cancer survivors of CNS tumours and leukaemia are at the greatest risk of cerebrovascular hospitalisations and more specifically hospitalisations due to cerebral haemorrhage and ischaemic stroke. Cranial irradiation is a strong risk factor associated with survivors being hospitalised for cerebrovascular complications. A risk-stratified approach to clinical follow-up, would ensure survivors at highest risk of cerebrovascular complications undergo surveillance. Further research is needed in survivors who have been diagnosed more recently where the use cranial irradiation may have changed or doses may differ to see if the risk of cerebrovascular disease is still elevated.

Table 4.1 Observed and expected numbers of cerebrovascular hospitalisations overall, standardised hospitalisation ratios and absolute excess risks, adjusted relative risks and excess hospitalisation ratios

	Number of 5-year survivors	Person-years	O/E	SHR (95%CI)	RR (95%CI)†	AER (95%CI)	EHR (95%CI)†
Overall	27,839	312868.7	299/59.0	5.1 (4.5-5.7)		7.7 (6.9-8.5)	
Gender							
Male	15216	170155.0	167/35.6	4.7 (4.0-5.5)	1.0 (referent)	7.7 (6.4-9.4)	1.0 (referent)
Female	12623	142713.7	132/23.4	5.6 (4.7-6.7)	1.2 (0.9-1.5)	7.6 (6.2-9.4)	0.9 (0.7-1.2)
$P_{heterogeneity}$				0.12	0.28	0.92	0.57
Attained age							
<20	7731	109400.4	52/3.4	15.5 (11.8-20.4)	1.0 (referent)	4.4 (3.3-5.9)	1.0 (referent)
20-29	8642	93476.3	55/7.2	7.6 (5.9-9.9)	0.5 (0.4-0.8)	5.1 (3.8-6.9)	1.1 (0.6-1.7)
30-39	5357	61643.4	77/11.3	6.8 (5.5-8.6)	0.6 (0.3-1.0)	10.7 (8.2-13.9)	2.1 (1.1-4.0)
40-49	3814	32555.1	55/15.8	3.5 (2.7-4.5)	0.3 (0.2-0.6)	12.0 (8.3-17.4)	2.4 (1.1-5.4)
≥50	2295	15793.5	60/21.4	2.8 (2.2-3.6)	0.4 (0.2-0.8)	24.5 (16.5-36.2)	5.4 (2.0-14.4)
P_{trend}				<0.001	<0.01	<0.001	0.01
Childhood Cancer							
Leukaemia	8374	91163.7	48/8.6	5.6 (4.2-7.4)	2.3 (1.0-5.0)	4.3 (3.1-6.1)	4.2 (0.8-23.7)
Hodgkin's disease	1759	20458.6	12/5.6	2.2 (1.2-3.8)	1.7 (0.6-4.3)	3.1 (1.1-9.0)	1.7 (0.2-14.7)
Non-Hodgkin's lymphoma	1274	15163.4	6/3.7	1.6 (0.7-3.7)	1.2 (0.4-3.7)	1.6 (0.2-11.9)	0.9 (0.0-18.9)
Central Nervous System tumour	6401	68269.3	186/15.6	11.9 (10.3-13.7)	8.5 (3.9-18.3)	25.0 (21.3-29.2)	19.5 (3.5-106.7)
Neuroblastoma	1281	14380.7	5/2.0	2.5 (1.1-6.1)	1.5 (0.5-4.7)	2.1 (0.5-9.0)	2.8 (0.4-21.2)
Non Heritable retinoblastoma	872	11257.4	4/3.0	1.3 (0.5-3.6)	1.0 (0.3-3.5)	0.9 (0.0-41.0)	0.0 (0.0,.)
Heritable retinoblastoma	604	7680.3	0/2.1	0.0 (.,.)	0.0 (0.0,.)	0.0 (0.0,.)	0.0 (0.0,.)
Wilms	2034	24756.4	7/4.1	1.7 (0.8-3.6)	1.0 (referent)	1.2 (0.2-7.0)	1.0 (referent)
Bone sarcoma	968	10948.6	7/3.3	2.1 (1.0-4.5)	1.8 (0.6-5.1)	3.4 (0.8-13.7)	2.4 (0.3-21.2)
Soft tissue sarcoma	1730	20430.5	14/5.0	2.8 (1.7-4.8)	2.1 (0.8-5.3)	4.4 (2.0-10.0)	4.1 (0.7-25.5)
Others	2542	28359.9	10/6.4	1.6 (0.9-2.9)	1.2 (0.4-3.1)	1.3 (0.2-7.0)	1.1 (0.1-10.3)
$P_{heterogeneity}$				<0.001	<0.001	<0.001	<0.001
Decade of diagnosis							
<1970	2488	35815.5	81/29.4	2.8 (2.2-3.4)	1.0 (referent)	14.4 (10.2-20.3)	1.0 (referent)
1970-1979	3791	56387.2	80/14.6	5.5 (4.4-6.8)	1.6 (1.0-2.5)	11.6 (8.9-15.2)	1.5 (0.8-2.7)
1980-1989	5761	86651.6	69/9.2	7.5 (5.9-9.5)	1.9 (1.1-3.3)	6.9 (5.3-9.1)	1.5 (0.7-3.0)
1990-1999	8659	102862.8	55/4.8	11.4 (8.8-14.9)	2.0 (1.0-4.0)	4.9 (3.7-6.5)	1.2 (0.5-2.9)
2000-2006	7140	31151.7	14/1.0	13.6 (8.1-23.0)	1.9 (0.8-4.6)	4.2 (2.4-7.3)	1.0 (0.4-2.9)
P_{trend}				<0.001	0.11	<0.001	0.47
Age at diagnosis							
0-4	12885	148050.3	89/19.4	4.6 (3.7-5.7)	1.0 (referent)	4.7 (3.6-6.1)	1.0 (referent)
5-9	7375	82371.7	112/15.0	7.5 (6.2-9.0)	1.1 (0.8-1.5)	11.8 (9.5-14.6)	1.3 (0.9-1.9)
10-14	7579	82446.7	98/24.7	4.0 (3.3-4.8)	0.7 (0.5-1.0)	8.9 (6.8-11.6)	0.9 (0.6-1.4)
P_{trend}				0.22	0.03	<0.001	0.64

AER: absolute excess risk, CI: confidence interval, EHR: excess hospitalisation ratio, O/E: observed/expected, RR: relative risk, SHR: standardised hospitalisation ratio

† adjusted for gender, childhood cancer, attained age, age at diagnosis and decade of diagnosis

Table 4.2 Observed and expected numbers of cerebral haemorrhage hospitalisations standardised hospitalisation ratios and absolute excess risks, adjusted relative risks and excess hospitalisation ratios

	Number of 5-year survivors	Person-years	O/E	SHR (95%CI)	RR (95%CI)†	AER (95%CI)	EHR (95%CI)†
Overall	27,839	313793.5	104/12.9	8.1 (6.7-9.8)		2.9 (2.5-3.4)	
Gender							
Male	15216	170710.9	56/8.6	6.5 (5.0-8.5)	1.0 (referent)	2.8 (2.0-3.8)	1.0 (referent)
Female	12623	143082.6	48/4.3	11.1 (8.4-14.8)	1.7 (1.1-2.5)	3.1 (2.2-4.2)	1.2 (0.7-1.8)
$P_{heterogeneity}$				<0.01	<0.01	0.67	0.54
Attained age							
<20	7731	109460.4	31/1.5	21.4 (15.1-30.5)	1.0 (referent)	2.7 (1.9-3.9)	1.0 (referent)
20-29	8642	93622.3	20/2.2	9.2 (5.9-14.2)	0.6 (0.3-1.1)	1.9 (1.2-3.1)	0.8 (0.4-1.6)
30-39	5357	61894.7	29/2.5	11.4 (8.0-16.5)	1.2 (0.5-2.9)	4.3 (2.9-6.4)	2.4 (0.9-6.2)
40-49	3814	32745.4	12/3.0	4.0 (2.3-7.0)	0.7 (0.2-2.1)	2.7 (1.3-5.9)	1.9 (0.5-7.6)
≥50	2295	16070.6	12/3.7	3.2 (1.8-5.7)	1.0 (0.2-4.2)	5.2 (2.3-11.7)	5.4 (0.8-36.8)
P_{trend}				<0.001	0.49	0.21	0.31
Childhood Cancer							
Leukaemia	8374	91262.8	24/2.2	10.7 (7.2-15.9)	2.1 (0.6-6.9)	2.4 (1.5-3.7)	4.1 (0.3-54.1)
Hodgkin's disease	1759	20497.9	3/1.2	2.5 (0.8-7.8)	0.9 (0.2-4.6)	0.9 (0.1-5.8)	0.6 (0.0-72.1)
Non-Hodgkin's lymphoma	1274	15189.0	2/0.8	2.5 (0.6-10.1)	0.9 (0.1-5.2)	0.8 (0.1-7.9)	1.3 (0.0-38.0)
Central Nervous System tumour	6401	68866.6	62/3.3	18.6 (14.5-23.8)	6.0 (1.9-19.7)	8.5 (6.5-11.1)	13.8 (1.1-177.3)
Neuroblastoma	1281	14388.8	2/0.5	4.8 (1.1-17.9)	1.3 (0.2-8.0)	1.1 (0.2-6.4)	2.2 (0.1-50.0)
Non Heritable retinoblastoma	872	11276.4	2/0.6	3.4 (0.8-13.5)	1.4 (0.2-8.6)	1.2 (0.2-9.0)	0.1 (0.0-2260.0)
Heritable retinoblastoma	604	7680.3	0/0.4	0.0 (.,.)	0.0 (0.0,.)	0.0 (0.0,.)	0.0 (0.0,.)
Wilms	2034	24774.2	3/0.9	3.3 (1.1-10.3)	1.0 (referent)	0.8 (0.2-4.3)	1.0 (referent)
Bone sarcoma	968	10986.3	0/0.7	0.0 (., .)	0.0 (0.0,.)	0.0 (0.0,.)	0.0 (0.0,.)
Soft tissue sarcoma	1730	20474.6	4/1.0	3.9 (1.5-10.3)	1.4 (0.3-6.2)	1.5 (0.4-5.4)	2.7 (0.2-46.0)
Others	2542	28396.6	2/1.3	1.6 (0.4-6.2)	0.5 (0.1-3.1)	0.3 (0.0-12.3)	0.3 (0.0-74.2)
$P_{heterogeneity}$				<0.001	<0.001	<0.001	<0.001
Decade of diagnosis							
<1970	2488	36136.0	15/5.3	2.8 (1.7-4.7)	1.0 (referent)	2.7 (1.2-5.9)	1.0 (referent)
1970-1979	3791	56648.2	23/3.1	7.5 (5.0-11.3)	2.6 (1.0-6.8)	3.5 (2.2-5.6)	2.2 (0.6-8.0)
1980-1989	5761	86870.5	27/2.4	11.1 (7.6-16.1)	4.4 (1.4-13.6)	2.8 (1.9-4.3)	3.3 (0.8-13.9)
1990-1999	8659	102975.1	30/1.7	18.0 (12.6-25.7)	6.6 (1.8-24.4)	2.8 (1.9-4.0)	3.9 (0.8-19.4)
2000-2006	7140	31163.7	9/0.4	22.5 (11.7-43.2)	7.0 (1.6-31.0)	2.8 (1.4-5.5)	3.8 (0.7-22.4)
P_{trend}				<0.001	0.01	0.68	0.18
Age at diagnosis							
0-4	12885	148277.9	33/4.5	7.3 (5.2-10.2)	1.0 (referent)	1.9 (1.3-2.9)	1.0 (referent)
5-9	7375	82763.1	41/3.4	12.2 (9.0-16.6)	1.2 (0.8-2.1)	4.5 (3.3-6.3)	1.5 (0.8-2.6)
10-14	7579	82752.5	30/5.0	6.0 (4.1-8.6)	0.8 (0.4-1.4)	3.0 (2.0-4.6)	1.0 (0.5-2.0)
P_{trend}				0.45	0.35	0.06	0.97

AER: absolute excess risk, CI: confidence interval, EHR: excess hospitalisation ratio, O/E: observed/expected, RR: relative risk, SHR: standardised hospitalisation ratio

† adjusted for gender, childhood cancer, attained age, age at diagnosis and decade of diagnosis

Table 4.3 Observed and expected numbers of ischaemic stroke hospitalisations, standardised hospitalisation ratios and absolute excess risks, adjusted relative risks and excess hospitalisation ratios

	Number of 5-year survivors	Person-years	O/E	SHR (95%CI)	RR (95%CI)†	AER (95%CI)	EHR (95%CI)†
Overall	27,839	313674.1	118/22.8	5.2 (4.3-6.2)		3.0 (2.6-3.6)	
Gender							
Male	15216	170661.3	65/14.7	4.4 (3.5-5.7)	1.0 (referent)	2.9 (2.2-4.0)	1.0 (referent)
Female	12623	143012.8	53/8.2	6.5 (5.0-8.5)	1.2 (0.9-1.8)	3.1 (2.3-4.3)	1.0 (0.7-1.6)
$P_{heterogeneity}$				0.04	0.25	0.79	0.96
Attained age							
<20	7731	109491.8	10/0.7	14.3 (7.7-26.6)	1.0 (referent)	0.8 (0.4-1.7)	1.0 (referent)
20-29	8642	93665.9	23/1.9	11.9 (7.9-17.9)	0.7 (0.3-1.6)	2.2 (1.4-3.5)	2.4 (1.0-5.9)
30-39	5357	61850.2	33/3.6	9.2 (6.5-12.9)	0.6 (0.2-1.6)	4.8 (3.2-7.0)	6.1 (2.1-17.5)
40-49	3814	32716.4	22/6.0	3.6 (2.4-5.5)	0.3 (0.1-0.9)	5.0 (2.7-8.7)	9.0 (2.5-32.9)
≥50	2295	15949.8	30/10.5	2.8 (2.0-4.0)	0.2 (0.1-0.9)	12.2 (7.0-21.2)	21.8 (4.6-103.2)
P_{trend}				<0.001	0.04	<0.001	<0.001
Childhood Cancer							
Leukaemia	8374	91289.8	18/2.8	6.4 (4.1-10.2)	2.2 (0.6-7.6)	1.7 (1.0-2.9)	2.8 (0.7-1.6)
Hodgkin's disease	1759	20506.2	2/2.2	0.9 (0.2-3.6)	0.7 (0.1-4.4)	0.0 (0.0,.)	0.4 (0.0-26.8)
Non-Hodgkin's lymphoma	1274	15167.6	4/1.5	2.9 (1.1-7.7)	2.0 (0.4-9.0)	1.7 (0.4-7.8)	2.0 (0.2-22.5)
Central Nervous System tumour	6401	68787.2	73/6.2	12.0 (9.6-15.1)	8.4 (2.6-27.3)	10.0 (7.8-12.8)	13.1 (2.0-84.5)
Neuroblastoma	1281	14384.5	1/0.7	1.3 (0.2-9.6)	0.7 (0.1-6.9)	0.2 (0.0-349.7)	0.9 (0.0-20.6)
Non Heritable retinoblastoma	872	11274.0	2/1.2	1.7 (0.4-7.0)	1.1 (0.2-7.0)	0.7 (0.0-23.2)	0.0 (0.0,.)
Heritable retinoblastoma	604	7680.3	0/0.8	0.0 (.,.)	0.0 (0.0,.)	0.0 (0.0, .)	0.0 (0.0,.)
Wilms	2034	24778.7	3/1.5	2.0 (0.6-6.2)	1.0 (referent)	0.6 (0.1-5.8)	1.0 (referent)
Bone sarcoma	968	10950.1	3/1.3	3.0 (1.1-7.9)	2.5 (0.5-11.6)	2.4 (0.6-10.6)	2.5 (0.2-29.2)
Soft tissue sarcoma	1730	20464.7	3/2.0	2.5 (1.0-6.0)	1.8 (0.4-7.6)	1.5 (0.3-6.3)	2.3 (0.3-20.6)
Others	2542	28391.0	4/2.5	1.6 (0.6-4.4)	1.2 (0.3-5.5)	0.5 (0.0-6.8)	0.0 (0.0,.)
$P_{heterogeneity}$				<0.001	<0.001	<0.001	<0.001
Decade of diagnosis							
<1970	2488	35994.7	39/12.9	3.0 (2.2-4.1)	1.0 (referent)	7.2 (4.5-11.6)	1.0 (referent)
1970-1979	3791	56635.7	29/5.4	5.4 (3.8-8.0)	1.2 (0.6-2.4)	4.2 (2.7-6.5)	1.5 (0.6-3.6)
1980-1989	5761	86856.3	32/2.9	10.9 (7.7-15.4)	1.7 (0.7-4.1)	3.3 (2.3-4.9)	2.5 (0.9-7.3)
1990-1999	8659	103006.8	17/1.3	12.8 (8.0-20.6)	1.3 (0.4-4.2)	1.5 (0.9-2.5)	2.1 (0.6-7.6)
2000-2006	7140	31180.6	1/0.3	3.5 (0.5-25.0)	0.3 (0.0-3.2)	0.2 (0.0-3.5)	0.5 (0.0-6.5)
P_{trend}				<0.001	0.91	<0.001	0.52
Age at diagnosis							
0-4	12885	148295.3	34/7.1	4.8 (3.4-6.7)	1.0 (referent)	1.8 (1.2-2.8)	1.0 (referent)
5-9	7375	82679.9	50/5.7	8.8 (6.6-11.6)	1.2 (0.7-1.9)	5.4 (3.9-7.3)	1.2 (0.7-2.0)
10-14	7579	82698.9	34/10.0	3.4 (2.4-4.7)	0.6 (0.3-1.0)	2.9 (2.0-4.7)	0.5 (0.3-1.0)
P_{trend}				0.10	0.04	0.05	0.05

AER: absolute excess risk, CI: confidence interval, EHR: excess hospitalisation ratio, O/E: observed/expected, RR: relative risk, SHR: standardised hospitalisation ratio

† adjusted for gender, childhood cancer, attained age, age at diagnosis and decade of diagnosis

Table 4.4 Observed and expected numbers of cerebrovascular hospitalisation overall among Central Nervous System tumour survivors, standardised hospitalisation ratios and absolute excess risks, adjusted relative risks and excess hospitalisation ratios

	Number of 5-year survivors	Person-years	O/E	SHR (95%CI)	RR (95%CI)†	AER (95%CI)	EHR (95%CI)†
Overall	6401	68269.3	186/15.6	11.9 (10.3-13.7)		25.0 (21.3-29.2)	
Gender							
Male	3460	346432.4	108/9.4	11.5 (9.5-13.8)	1.0 (referent)	27.1 (22.0-33.3)	1.0 (referent)
Female	2941	31836.9	78/6.2	12.6 (10.0-15.7)	1.0 (0.8-1.4)	22.6 (17.7-28.7)	0.8 (0.6-1.2)
$P_{heterogeneity}$				0.54	0.80	0.26	0.30
Attained age							
<20	1647	21619.0	35/0.7	50.5 (36.3-70.4)	1.0 (referent)	15.9 (11.3-22.3)	1.0 (referent)
20-29	2056	19284.5	31/1.5	21.1 (14.8-30.0)	0.5 (0.3-0.8)	15.3 (10.6-22.2)	0.9 (0.5-1.6)
30-39	1064	13458.6	47/2.5	18.9 (14.2-25.2)	0.5 (0.2-1.0)	33.1 (24.5-44.7)	1.8 (0.8-3.9)
40-49	933	9058.7	34/4.5	7.6 (5.5-10.7)	0.2 (0.1-0.5)	32.6 (22.2-48.0)	1.8 (0.7-4.7)
≥50	701		39/6.5	6.0 (4.4-8.2)	0.2 (0.1-0.6)	67.0 (45.9-97.6)	3.9 (1.3-11.8)
P_{trend}				<0.001	<0.001	<0.001	0.11
Decade of diagnosis							
<1970	715	9758.1	54/8.6	6.3 (4.8-8.2)	1.0 (referent)	46.5 (33.9-63.9)	1.0 (referent)
1970-1979	874	12481.9	46/3.7	12.3 (9.2-16.4)	1.4 (0.8-2.4)	33.9 (24.7-46.3)	1.1 (0.6-2.1)
1980-1989	1092	15740.0	36/1.9	18.9 (13.7-26.3)	1.5 (0.7-3.0)	21.7 (15.3-30.6)	1.1 (0.5-2.3)
1990-1999	1979	22698.2	40/1.1	35.1 (25.7-47.8)	1.9 (0.8-4.6)	17.1 (12.4-23.6)	1.1 (0.4-2.8)
2000-2006	1741	7591.1	10/0.3	36.3 (19.6-67.5)	1.6 (0.5-4.8)	12.8 (6.8-24.2)	0.8 (0.2-2.6)
P_{trend}				<0.001	0.31	<0.001	0.18
Age at diagnosis							
0-4	1969	20797.0	39/2.8	13.9 (10.1-19.0)	1.0 (referent)	17.4 (12.4-24.4)	1.0 (referent)
5-9	2246	24311.6	76/5.3	14.5 (11.6-18.1)	1.2 (0.8-1.8)	29.1 (22.9-37.0)	1.5 (1.0-2.3)
10-14	2186	23160.7	71/7.6	9.4 (7.4-11.8)	0.9 (0.6-1.4)	27.4 (21.1-35.5)	1.2 (0.7-2.0)
P_{trend}				0.02	0.53	0.05	0.59

AER: absolute excess risk, CI: confidence interval, EHR: excess hospitalisation ratio, O/E: observed/expected, RR: relative risk, SHR: standardised hospitalisation ratio

† adjusted for gender,attained age, age at diagnosis and decade of diagnosis

Table 4.5 Observed and expected number of cerebrovascular hospitalisations overall among survivors diagnosed between 1940 and 1991, standardised hospitalisation ratios and absolute excess risks, adjusted relative risks and excess hospitalisation ratios

	Explanatory factor	Number of 5-year survivors	Person-years	O/E	SHR (95%CI)	RR (95%CI)†	AER (95%CI)	EHR (95%CI)†
Overall	No cranial irradiation	5775	85945.0	68/34.9	1.9 (1.5-2.5)	1.0 (referent)	3.9 (2.4-6.3)	1.0 (referent)
	Cranial irradiation	3675	53736.2	147/12.6	11.7 (9.9-13.7)	5.0 (3.7-6.8)	25.0 (21.0-29.8)	8.5 (5.1-14.1)
$P_{heterogeneity}$					<0.001	<0.001	<0.001	<0.001
CNS tumour	No cranial irradiation	892	13106.3	17/5.6	3.0 (1.9-4.9)	1.0 (referent)	8.7 (4.3-17.7)	1.0 (referent)
	Cranial irradiation	1361	18614.4	116/7.4	15.6 (13.0-18.9)	5.0 (3.0-8.3)	58.3 (48.0-70.8)	6.6 (3.3-13.1)
$P_{heterogeneity}$					<0.001	<0.001	<0.001	<0.001
Leukaemia	No cranial irradiation	198	2987.4	1/0.9	1.1 (0.2-7.7)	1.0 (referent)	0.3 (0.0-4910.0)	1.0 (referent)†
	Cranial irradiation	2291	34772.7	31/5.1	6.1 (4.3-8.6)	2.2 (0.3-16.2)	7.4 (4.9-11.4)	2.6 (0.1-63.3)
$P_{heterogeneity}$					0.06	0.39	0.13	0.43

AER: absolute excess risk, CNS: central nervous system, CI: confidence interval, EHR: excess hospitalisation ratio, O/E: observed/expected, RR: relative risk, SHR: standardised hospitalisation ratio

† adjusted for gender, attained age, age at diagnosis, decade of diagnosis, cranial irradiation

CHAPTER 5 RISK OF GENITOURINARY PRIMARY CANCERS SUBSEQUENT TO CHILDHOOD CANCER DIAGNOSED THROUGHOUT EUROPE: THE PANCARESURFUP COHORT

5.1 ABSTRACT

Background: Survivors of childhood cancer are at increased risk of developing subsequent primary neoplasms (SPNs). Cancers of the genitourinary (GU) system predominantly develop beyond age 40 years and few previous studies have investigated the long-term risks of developing such SPNs in childhood cancer survivors and none had adequate statistical power to investigate the risks of specific neoplasms such as bladder cancer or testicular cancer.

Methods: The European PanCareSurFup cohort comprising 75,217 five-year survivors of childhood cancer, diagnosed below the age of 20 years, was investigated to determine the absolute and excess risks of genitourinary SPNs. The excess risks of genitourinary SPNs were quantified by standardised incidence ratios (SIR) and absolute excess risks (AER) per 10,000 person-years. Cumulative incidence of developing a first genitourinary SPN was estimated treating death as a competing risk.

Results: After a mean follow-up time of 20.7 years, 277 (0.37%) genitourinary SPNs were diagnosed among 75,217 survivors of childhood cancer. The most commonly observed genitourinary SPNs were of the kidney (n=70), bladder (n=44) and testis (n=38). Overall, survivors were twice as likely to develop a genitourinary SPN of any type than expected (SIR=1.7, 95%CI:1.5-1.9, AER=1.0, 95%CI:0.8-1.2). Survivors of retinoblastoma (SIR=3.5, 95%CI:2.3-5.3) and Wilms' tumour (SIR=3.3, 95%CI:2.3-4.8) were at the greatest risk of developing any genitourinary SPN. Overall, survivors had a 5-fold expected risk of developing a kidney SPN (SIR=5.2, 95%CI:4.1-6.6) and a 4-fold expected risk of developing a bladder SPN (SIR=3.7, 95%CI:2.7-4.9). Male survivors were not at a significantly increased risk of developing a testicular SPN (SIR=0.8, 95%CI:0.6-1.0).

Conclusion: This study, the largest ever undertaken, found survivors of retinoblastoma and Wilms' tumour at particular increased risk of developing genitourinary SPNs. The former group of survivors are at increased risk of developing bladder SPNs while the latter are at

increased risk of developing kidney SPNs. It is important that health professionals involved in the long-term follow-up care of childhood cancer survivors are aware of the excess risks of genitourinary SPNs as survivors become older so they may provide information accordingly and counsel survivors in relation to early symptoms.

5.2 INTRODUCTION

Survival after childhood cancer has continued to improve in recent decades, with the most recent overall five-year survival being approximately 80% in developed countries (39, 236). Due to advances in treatment, the population of childhood cancer survivors across Europe surviving to at least five years is increasing (237-239). It is estimated that the number of childhood cancer survivors across Europe is currently between 300,000 and 500,000 (240). However, this growing population of survivors of childhood cancer is at risk of a spectrum of adverse health outcomes related to the cancer or its treatment (241). The most common cause of premature mortality among mature survivors is the development of subsequent primary neoplasms (SPNs) (60). Most survivors can now expect to live many decades and increasing numbers of survivors are reaching ages at which in the general population the risk of cancer typically starts to increase inexorably. Cancers of the digestive tract and genitourinary system predominantly develop at older ages and few previous studies have investigated the long-term risks of developing such primary neoplasms in childhood cancer survivors. To our knowledge, none had adequate statistical power to investigate the risks of specific cancers such as bladder cancer or testicular cancer. No large scale study has been conducted investigating the risk of genitourinary SPNs collectively.

In 2011 a large European collaborative study funded by the 7th Framework Programme of the European Union called PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies (PanCareSurFup) was established. PanCareSurFup is a consortium of 16 European institutions in 12 countries established in February 2011 and funded by the 7th Framework Programme of the European Commission (www.pancaresurfup.eu) (173). The global aim of PCSF consortium is to conduct studies into long-term complications of treatment for cancer, to establish guidelines for clinical follow-up of survivors, and to disseminate the results and provide training and workshops for stakeholders. One of the

objectives of PanCareSurFup was to investigate the risk of SPNs that are common in the general population after the age of 40 years through a retrospectively ascertained European cohort of childhood cancer survivors from 12 different countries across Europe.

The aim of the current study was to investigate the risk of developing subsequent primary genitourinary (GU) neoplasms in five-year survivors of childhood cancer using the greatest number of long-term survivors ever assembled from pooling across the 10 countries involved.

5.3 METHODS

5.3.1 PanCareSurFup

The study comprises 11 European cohorts (across 10 countries) of survivors of childhood cancer diagnosed with a first primary neoplasm (FPN) below 20 years of age. A total of 75,217 individuals surviving at least five years after childhood cancer were included ascertained from population-based cancer registries or major treatment centres across 10 different countries within Europe. Data collected from each cohort was sent to the coordinating centre at the University of Mainz, Germany for initial cleaning of the data. The entire dataset was subsequently transferred to the University of Birmingham, UK, for further consistency checks and statistical analyses. Ethical approval for the study was obtained for each contributing cohort separately. Table 5.1 describes the main characteristics of each specific cohort forming the overall European PanCareSurFup cohort.

5.3.2 Case identification, ascertainment & validation

First primary neoplasms (FPNs)

First primary neoplasms (FPNs) were mostly coded in International Classification of Diseases for Oncology (ICD-O)-1, 2, 3 (242-244) and were aggregated into groups by type of childhood cancer as defined in the International Classification of Childhood Cancer (ICCC) (12) through a conversion programme developed by the International Agency for Research on

Cancer (IARC) (245, 246). A large proportion of FPNs provided by both Norway and Slovenia were classified only in International Classification of Diseases (ICD)-7 (247) format therefore due to a lack of morphological detail, conversion to ICCC groups was not possible and hence these countries were excluded from the current cohort analysis. Furthermore any other FPNs with insufficient information for the IARC conversion programme were also excluded from the analysis.

Ascertainment of subsequent primary neoplasms (SPNs)

Since the focus of this study was on genitourinary SPNs, which are solid cancers, known to have strong associations with radiation exposure and characterised by latency periods of 10 or more years (248), only SPNs developing after five-year survival were considered. SPNs were ascertained largely through population-based cancer registries (Denmark, Finland, Iceland, Sweden, Switzerland and UK), questionnaires to the survivor and/or their families (France, Hungary, Netherlands and Switzerland) or late effect clinics (Hungary and Switzerland). Other methods of ascertainment included linkage to health insurance registries (France), linkage to hospital data or medical records (Italy, Netherlands), cancer registrations (Netherlands) or linkage with mortality statistics (Italy and Switzerland). SPNs were validated by obtaining pathology reports or other clinical documentation. For SPNs to be included in this study they had to be malignant if developing outside the CNS, benign or malignant if developing within the CNS and any tumour of the bladder was included. All ascertained SPNs were coded according to the ICD-O (242-244) or ICD (224, 247, 249, 250) or both. Where countries provided SPN information in both ICD-O and ICD format, the former took precedence. ICD categories were taken from the definition used in Reulen *et al* (63). Table 5.2 provides the ICD-O codes used to define site-specific GU SPNs while Table 5.3 provides the ICD codes used to define these same SPNs. Only GU SPNs that were malignant were

included in the analysis with the exception of bladder SPNs, for which malignant, benign, uncertain behaviour and carcinoma in-situ behaviour codes were all included. Problems with the histological differentiation of malignant, benign, uncertain behaviour and in-situ histology at the site of the bladder are known (251) .

5.3.3 General population cancer rates

An attempt was made to obtain site-based (ICD-10) general population cancer rates for each country via several different sources. General population cancer rates for specified calendar-years were downloaded from the European Cancer Observatory (ECO) hosted by the International Agency for Research on Cancer (IARC) (252) for Denmark, Sweden (1960-2009) and Iceland (1955-2007). Finnish cancer rates from 1953-2011 were obtained from Statistics Finland (253). The Office for National Statistics (ONS) provided cancer rates from 1971-2006 for the UK general population (254) . Cancer rates from the Swiss general population were provided by the Swiss National Institute for Cancer Epidemiology and Registration (NICER) for the calendar-years 1985 to 2011 (255). The UK cancer rates were used for countries for which general population cancer rates were unattainable. For countries where the range of calendar-years for the general population cancer rates did not match that of the period of SPN ascertainment in the PCSF cohort, rates from the closest available year were used as a proxy.

5.3.4 Statistical methods

The period at risk of developing a SPN was initiated five years following initial diagnosis of childhood cancer until the first occurrence of loss to follow up, death, GU SPN of interest, or reaching the end of follow-up. Multiple SPNs per survivor were permitted for comparisons with the general population to avoid bias. Standardised incidence ratios (SIRs) were calculated as the observed SPNs divided by the expected number of neoplasms in the

underlying cohort. The expected numbers of cancers in each cohort were calculated by multiplying general population cancer incidence rates (stratified by sex, 5-year age bands, and 1-year calendar bands) by the accumulated person-years within each corresponding sex, age and calendar year stratum in the PCSF cohort and summing as appropriate. Absolute excess risks (AERs) were calculated as the observed minus expected divided by the number of person-years at risk multiplied by 10,000. Relative risks of developing a SPN by sex, childhood cancer type, attained age, country of diagnosis, time since five-year survival, decade of diagnosis and age at diagnosis were derived using a multivariable Poisson regression model that incorporated the expected number of cancers as the log-offset. Two separate multivariable models were fitted, one adjusting for attained age and another adjusting for time since five-year survival, because of collinearity between these two factors. Cumulative incidence of developing a first GU SPN of interest was estimated by treating death as a competing risk. For SPN subtypes that exceeded 30 observed events we also evaluated the SIRs and AERs by sex, childhood cancer and attained age. Statistical significance was taken at the 5% level (two sided tests). Analyses were carried out using Stata statistical software (version 13.0; Stata Corp., College Station, TX).

5.4 RESULTS

5.4.1 Cohort characteristics

Overall, 277 (0.37%) genitourinary subsequent primary neoplasms (SPNs) were diagnosed among the 75,217 five-year survivors of childhood cancer. Total follow-up subsequent to five-years was 1,179,332 person-years. The mean follow-up time from childhood cancer diagnosis was 20.7 years (median, 18.9 years; range: 5.0-66.6 years). The most commonly observed genitourinary SPNs were of the kidney (n=70), bladder (n=44) and testis (n=38) (Table 5.5). Genitourinary SPNs occurred most frequently in survivors who were originally

diagnosed with 'other' neoplasms (n=60), CNS tumours (n=47) and soft tissue sarcoma tumours (n=33) (Table 5.5).

5.4.2 Overall Risk of Genitourinary Subsequent Primary Neoplasm (Table 5.4)

Survivors were twice as likely to develop a genitourinary SPN than expected (SIR=1.7, 95%CI:1.5-1.9) with an absolute excess risk of 1.0 SPN per 10,000 person-years (95%CI:0.8-1.2). The SIRs for attained age did not vary significantly across the age-groups however the AER increased significantly (P_{trend}<0.001) from 0.3 genitourinary SPNs per 10,000 person-years among survivors aged <20 years to 9.7 genitourinary SPNs per 10,000 person-years among survivors aged ≥50 years respectively. Survivors of retinoblastoma (SIR=3.5, 95%CI:2.3-5.3) and Wilms' tumour (SIR=3.3, 95%CI:2.3-4.8) were at the greatest risk of developing a genitourinary SPN with 3 and 2 excess SPNs per 10,000 person-years respectively. Childhood cancer type was a significant factor ($P_{heterogeneity}$<0.01) in the risk of developing a genitourinary SPN. The AERs showed a decreasing trend (P_{trend}<0.01) with more recently diagnosed childhood cancer survivors; those diagnosed between 1970 and 1979 had 1.4 excess SPNs (95%CI:0.8-2.5) per 10,000 person-years while those diagnosed in 2000 or later had no excess SPNs. Survivors aged between 0 and 4 years at cancer diagnosis were twice as likely than expected to develop a genitourinary SPN while survivors aged between 15 and 19 years at cancer diagnosis were almost comparable with that expected from the general population (P_{trend}<0.001). When exploring the risk of developing a genitourinary SPN by country (of those contributing to the PanCareSurFup cohort), survivors in France (SIR=3.4, 95%CI:2.4-5.0), Hungary (SIR=2.7, 95%CI:1.5-5.1) and the Netherlands (SIR=2.3, 95%CI:1.6-3.4) had the highest risks; the AER was 3.1 (95%CI:1.8-5.1), 1.3(95%CI:0.5-3.4) and 1.4 (95%CI:0.7-2.7) per 10,000 person-years in each of these countries respectively. The multivariable Poisson models revealed that childhood cancer type, country of diagnosis,

decade of diagnosis and time since five-year survival were all significantly associated with the risk of developing a genitourinary SPN.

The cumulative risk of developing a genitourinary SPN increased from 0.14% (95%CI:0.11-0.18) by 20 years from childhood cancer diagnosis to 0.98% (95%CI:0.82-1.15) by 40 years from diagnosis whereas 0.7% was expected from the general population at this time point (Figure 5.1). With respect to childhood cancer type, the cumulative risk of developing a genitourinary SPN by 40 years from original cancer diagnosis was highest at 1.64% among soft tissue sarcoma survivors and 1.54% among NHL survivors respectively. Survivors of CNS tumours had the lowest cumulative risk (0.53%) of developing a genitourinary SPN by 40 years from their original childhood cancer diagnosis (Figure 5.2). Survivors in France had the highest cumulative risk by 40 years from childhood cancer diagnosis, 1.51% closely followed by survivors from Denmark (1.21%), Finland (1.20%) and Sweden (1.08%). Survivors in the UK had a cumulative risk of 0.98% by 40 years from cancer diagnosis (Figure 5.3).

5.4.3 Genitourinary site specific subsequent primary neoplasms (Table 5.6)

Analyses by site of SPN revealed that compared to expected survivors were at greatest risk of developing neoplasms of the kidney (SIR=5.2, 95%CI:4.1-6.6) and bladder (SIR=3.7, 95%CI:2.7-4.9). Female survivors were also at significantly increased risk of developing female site specific neoplasms including corpus uteri (SIR=2.7, 95%CI:1.9-3.9), ovary (SIR=1.7, 95%CI:1.2-2.3) and other female sites (e.g. vulva, vagina) (SIR=3.4, 95%CI:2.0-5.7). Male survivors were however not at significantly increased risks of developing male site specific neoplasms including testis (SIR=0.8, 95%CI:0.6-1.0), prostate (SIR=1.3, 95%CI:0.8-2.0) or penis (SIR=0.9, 95%CI:0.1-6.3). The absolute excess risks for all of the genitourinary sites were between 0.1 and 0.5 SPNs per 10,000 person-years.

5.4.4 Subsequent primary neoplasms of the kidney (Table 5.7)

Inspection of the SIRs by childhood cancer type revealed survivors of Wilms' tumour (SIR=25.7, 95%CI:15.7-41.9) and neuroblastoma (SIR=14.4, 95%CI:6.0-34.5) to be at substantially increased risk of developing a kidney SPN compared to that expected. Although to a lesser extent, survivors of others (SIR=7.0, 95%CI:4.5-10.7), NHL (SIR=6.0, 95%CI:2.5-14.5), Hodgkin's disease (SIR=5.3, 95%CI:2.5-11.2), leukaemia (SIR=3.8,95%CI:1.6-9.2) and soft-tissue sarcoma (SIR=3.8, 95%CI:1.6-9.2) also appeared to be at increased risk of developing a subsequent primary kidney neoplasm. The SIR decreased with increasing attained age ($P_{trend}<0.001$), yet the AERs increased with increasing attained age ($P_{trend}<0.001$) with survivors aged 50 or older experiencing an excess of 4 kidney SPNs per 10,000 person-years. The cumulative risks of developing a kidney SPN 50 years from the original childhood cancer diagnosis was 0.6% whereas 0.2% was expected based on general population incidence rates for kidney neoplasms (Figure 5.4).

5.4.5 Subsequent primary neoplasms of the bladder (Table 5.7)

Survivors of retinoblastoma (SIR=19.7, 95%CI:10.2-37.8) were at the greatest risk of developing a bladder SPN, with survivors of leukaemia (SIR=11.3, 95%CI:5.7-22.6) and neuroblastoma (SIR=10.4, 95%CI:2.6-41.6) experiencing risks greater than 10-fold that expected. The SIRs decreased with increasing attained age ($P_{trend}<0.001$), whilst the AER increased although the AER remained below 1 excess bladder cancer per 10,000 person-years even after age 50 (AER=0.8, 95%CI: 0.1-9.6). The cumulative risks of developing a bladder subsequent primary neoplasm 50 years from the original childhood cancer diagnosis was 0.5% whereas 0.2% was expected (Figure 5.5).

5.4.6 Subsequent primary neoplasms of ovary (Table 5.7)

Although the overall risk of developing a subsequent primary tumour of the ovary was 1.7 (95%CI:1.2-2.3) the risk was confined to survivors of a CNS tumour (SIR=3.1, 95%CI:1.9-5.2). The AER was however relatively small, even for CNS survivors (AER= 0.4, 95%CI:0.2-0.9).

5.4.7 Subsequent primary neoplasms of testis (Table 5.7)

The SIR of developing a neoplasm of the testis did not appear to vary with childhood cancer type ($P_{heterogeneity}$=0.13); in fact, no type of childhood cancer appeared to be at significantly increased risk. Similarly, the SIR did not vary by attained age either (P_{trend}=0.50).

5.5 DISCUSSION

This is the first study ever to satisfactorily investigate the risk of specific genitourinary SPNs in survivors of childhood cancer. We show that, relative to the general population, survivors of childhood cancer are at increased risk of developing genitourinary SPNs, particularly of the kidney and bladder. We further demonstrate, for the first time, that survivors were at similar risk of developing neoplasms of the testis as the general population and that survivors of a CNS tumour are at increased risk of developing an ovarian subsequent primary neoplasm.

Comparing our findings to previous studies is difficult since very few studies investigated the risks of genitourinary SPNs in survivors of childhood cancer and, at least to our knowledge, in all previous studies the actual number of SPNs was very limited; the largest previous study to date—the North American Childhood Cancer Survivor Study (CCSS)—included 25 genitourinary SPNs compared to 277 genitourinary SPNs in the current study (67). In this study, survivors of retinoblastoma and Wilms' tumour were at the greatest risk of developing a genitourinary SPN. However, in the CCSS (67) no genitourinary SPNs were identified

among Wilms tumour survivors, but this finding is nonetheless not inconsistent with our findings considering the high upper confidence interval limit reported.

5.5.1 Subsequent primary neoplasm of the kidney

In this study, the risk of developing a kidney SPN was 5-fold that expected. Wilson *et al* (256) reported an 8-fold expected risk of developing kidney carcinomas after childhood cancer which is similar to our findings. In our study, survivors of a Wilms tumour in particular were at increased risk. The risk is likely related to previous treatment with flank or abdominal irradiation, but exposure to specific chemotherapeutic agents, particularly platinum based compounds, might increase the risk as well (256). In our study, survivors of neuroblastoma also had a much higher risk than expected of developing a kidney SPN. Consistent with this, an elevated risk among childhood cancer survivors developing renal cell carcinoma after neuroblastoma has been observed in the CCSS (67, 256). However, the pathophysiology between renal cell carcinoma after neuroblastoma has been reported to be poorly understood (67).

5.5.2 Subsequent primary neoplasm of the bladder

In this study, the multiplicative risk of developing bladder cancer following childhood cancer compared to that expected from the general population was substantially elevated; nonetheless this substantially elevated risk did not translate into a substantially increased absolute excess risk—even beyond age 50 years the absolute excess risk was less than 1 per 10,000 person-years. We are not able to compare these findings to previous studies since very little literature relates to the risk of bladder cancer after childhood cancer, most likely because the risk of bladder cancer in the background population only starts to increase beyond age 50 and thus most studies would have had very few bladder cancers. To our knowledge, the only study not included in the current collaborative study reporting on bladder cancer after childhood cancer

was the CCSS study (67), but this study only included five bladder cancers demonstrating the clear need for large-scale collaborative studies such as the current one. Both previous treatment with high-dose cyclophosphamide and exposure to high dose abdominal irradiation have been implicated in causing bladder cancer, but only at high doses and after cancer beyond age 40 years (257). Thus far, no study has reported an increase in bladder cancer after childhood cancer with the exception of a study by Frobisher *et al* (258) who reported an increased risk of bladder cancer in a British cohort based on 17 bladder cancers, all of which were also included in the current collaborative study. Survivors of retinoblastoma had particularly high risks of developing a bladder SPN in this study. A BCCSS study previously demonstrated high risks of bladder SPNs after heritable retinoblastoma (258). Since we could not distinguish between heritable and non-heritable retinoblastoma in the current study, we were not able to confirm this, but it is possible that the high risk of bladder cancer observed is partially attributable to the genetic predisposition (e.g. RB-1 gene) among survivors of heritable retinoblastoma. Previous studies of retinoblastoma survivors have demonstrated the influence of genetic predisposition on the risk of developing SPNs (259-262). Another possible explanation of such a finding is treatment with cyclophosphamide in survivors of heritable retinoblastoma. A Dutch study demonstrated that survivors of heritable retinoblastoma treated with chemotherapy, which potentially included cyclophosphamide developed bladder cancers and these did not develop until survivors were aged at least 30 years or older (263). The effect of cyclophosphamide on the bladder is known hence patients treated with this drug are given Mesna to protect their bladder lining (164, 264, 265).

5.5.3 Subsequent primary neoplasm of the testis

To our knowledge, no previous study satisfactorily evaluated the risks of developing cancer of the testis after childhood cancer. Inskip *et al* (266) reported a 2-fold increased risk compared

to expected, but this was only based on 12 observed SPNs. In general, very few epidemiological studies have evaluated the association between ionizing radiation and development of testicular cancer, but the few studies that did—including studies among Japanese atomic bomb survivors—did not find an excess of testicular cancer among individuals exposed to ionizing radiation (267). Overall, the available evidence from epidemiological studies thus far suggests that the testis is probably insensitive to the mutagenic effect of ionizing radiation; however, this has not been empirically demonstrated in survivors of childhood cancer. Most previous epidemiological studies have related to adults exposed to low doses of radiation from diagnostic procedures (e.g. X-rays), occupational or environmental exposures. The risk of developing testicular cancer after exposure of the testis to high doses of ionizing radiation in childhood has not been evaluated. Many survivors of childhood cancer will have received much higher doses of radiation to the testis than in such previous studies. Here we provide, for the first time, evidence for an absence of an increased risk of testicular cancer among survivors of childhood cancer. Further studies are, however, necessary to evaluate the risk, or lack thereof, by specific cumulative radiation doses to the testis and by cumulative doses of specific chemotherapeutic agents. Perhaps, if there is an increased risk, it may only become apparent after exposure of the testis to very high doses of radiation.

5.5.4 Subsequent primary neoplasm of the ovary

We found, to our knowledge for the first time that survivors of a CNS tumour are at increased risk of developing a SPN of the ovary. No other types of childhood cancer were at increased risk. A possible explanation for this increased risk may be previous treatment with cranial irradiation damaging the pituitary gland and affecting the hypothalamic-pituitary-gonadal-axis causing hormonal imbalances in luteinising hormone (LH) and follicle stimulating hormone

(FSH) subsequently leading to a need for hormone replacement therapy. Treatment with hormone replacement therapy is a recognised risk factor for developing ovarian cancer (268, 269). Nonetheless, the exact reason for the increased risk in CNS tumour survivors remains elusive and the possibility of this association being a chance finding should not be entirely excluded.

5.5.5 Study limitations

A possible limitation of this study is the lack of available treatment information for the majority of survivors in the cohort. Many of the countries contributing data to this study are based on population-based cohorts using data from cancer registries which generally do not routinely collect treatment as part of the cancer registration process. However, the risks of developing a genitourinary SPN in relation to treatment will be further investigated with nested-case control studies as part of the PanCareSurFup project whereby detailed radiation dosimetry and cumulative doses of chemotherapeutic drugs will be collected for each survivor.

Another potential limitation relates to significant heterogeneity in SIRs and AERs between the different countries contributing to this overall study. Survivors treated in France and the Netherlands were at greatest risk of developing a genitourinary SPN. Both the French and Dutch cohorts were treatment-centre based (as compared to population-based cohorts) with major referral centres included. Ascertainment of survivors for inclusion in late effect follow-up cohorts through treatment centre based hospitals might be problematic because it is not inconceivable that survivors previously treated with less intense treatment regimens are more likely to be lost to follow-up than those who were treated with more intense treatment regimens and regularly attend follow-up clinics at such treatment based centres. There may also be international variation between population-based cohort and treatment centre based

cohorts in terms of clinical trials that childhood cancer survivors are entered into. The biological way in which treatment affects a childhood cancer survivor of the same height and weight between a population-based cohort and treatment centre based cohort is unlikely to vary, however the total cumulative dose of chemotherapy, type of chemotherapy and radiotherapy regimens given between clinical trials could certainly vary, which may account for the differences in GU SPN development among survivors in population-based cohorts compared to survivors in treatment-centre based cohorts. Differences in treatment regimens between population-based and treatment centre based cohorts will be explored further in nested case-control studies that are being conducted as part of the PanCareSurFup project.

A third potential limitation is that we were not able to distinguish between survivors diagnosed with heritable and non-heritable retinoblastoma in the current PanCareSurFup cohort. Previous studies have reported substantially increased risk of genitourinary SPNs after a diagnosis of heritable retinoblastoma, but no increased risks after, or to a much lesser extent, after non-heritable retinoblastoma. Therefore, the substantially increased risks of GU SPNs we observe after retinoblastoma are most likely to be confined to heritable retinoblastoma survivors.

5.5.6 Conclusion

In conclusion, this study, the largest ever undertaken to comprehensively investigate genitourinary SPNs among childhood cancer survivors demonstrates, for the first time, that survivors are at similar risk of developing neoplasms of the testis as the general population and that survivors of a CNS tumour are at increased risk of developing an ovarian SPN. We further show that, relative to the general population, survivors of childhood cancer are at increased risk of developing genitourinary SPNs, particularly of the kidney and bladder. Survivors groups at particular increased risk of developing a genitourinary SPN are

retinoblastoma and Wilms' tumour, the former are at increased risk of developing bladder SPNs while the latter are increased risk of developing a kidney SPN. It is important that health professionals involved in the long-term follow-up care of childhood cancer survivors are aware of the excess risks of genitourinary SPNs as survivors become older so they may provide information accordingly and counsel survivors in relation to early symptoms. As screening is not widely available for all genitourinary cancers, in the UK for instance, there is only a national screening programme for cervical cancer, it will also be necessary for healthcare professionals to raise awareness among survivors about risk factors such as smoking which is strongly associated with bladder cancer and also a risk factor for kidney cancer. Promoting healthy lifestyle behaviours in addition to counselling survivors about early symptoms ought to be considered simultaneously when advising childhood cancer survivors about second primary genitourinary cancers.

Table 5.1 Description of cohorts and first primary neoplasm characteristics

Cohort	No. of 5-year survivors	study design	period of FPN diagnosis	age at FPN diagnosis	End of follow-up	type of FPNs	inclusion criteria
France	3,037	treatment centre	1946-1986	<16 yrs	Sept 2014	all except leukaemia	malignant or intracranial
Hungary	4,873	Population-based	1971-2008	<16 yrs	Dec 2014	all childhood cancers	malignant of intracranial
Italy	10,833	Population-based	1964-2009	<18 yrs	Jan 2012	all childhood cancers	malignant or intracranial
Italy	9,136	treatment centre	1960-2008	<18 yrs	Dec 2014	all childhood cancers	malignant or intracranial
Netherlands	6,075	treatment centre	1963-2002	<18 yrs	Dec 2012	all malignant plus benign CNS	malignant or intracranial
Denmark	4,781	Population-based	1943-2005	<20 yrs	Dec 2003	all malignant plus benign CNS	malignant, intracranial or of bladder
Sweden	7,710	Population-based	1958-2003	<20 yrs	Dec 2003	all malignant plus benign CNS	malignant, intracranial or of bladder
Iceland	274	Population-based	1955-2003	<20 yrs	Dec 2003	all malignant plus benign CNS	malignant, intracranial or of bladder
Finland	6,150	Population-based	1953-2011	<20 yrs	Dec 2012	all malignant plus benign CNS	malignant, intracranial or of bladder
Switzerland	4,390	Population-based	1976-2005	<20 yrs	Jan 2014	all childhood cancers	malignant or intracranial
UK	17,958	Population-based	1940-1991	<15 yrs	Dec 2006	all malignant plus benign CNS	malignant, intracranial or of bladder

FPN: first primary neoplasm

Table 5.2 ICD-O topography codes used to classify site specific genitourinary subsequent primary neoplasms

Subgroups	ICD-O-1	ICD-O-2	ICD-O-3
Bladder	1880-1889	C67.0-C67.9	C67.0-C67.9
Cervix Uteri†	1800-1809	C53.0-C53.9	C53.0-C53.9
Corpus Uteri†	1820-1828	C54.0-C54.9	C54.0-C54.9
Kidney	1890-1899	C64.9-C66.9,C68.0-C68.9	C64.9-C66.9,C68.0-C68.9
Other female sites†	1799,1819,1840-1849	C51.0-C52.9, C55.9, C57.7, C57.8, C57.9, C58.9	C51.0-C52.9, C55.9, C57.7, C57.8, C57.9, C58.9
Ovary†	1830	C56.9	C56.9
Penis‡	1871-1874	C60.0-C60.9	C60.0-C60.9
Prostate‡	1859	C61.9	C61.9
Testis‡	1860,1869	C62.0-C62.9	C62.0-C62.9

† Female sites only
‡ male sites only

Table 5.3 ICD codes used to classify site specific genitourinary subsequent primary neoplasms

Subgroups	ICD-7	ICD-8	ICD-9	ICD-10
Bladder	1810-1819§	1880-1889, 223.3, 237.6	1880-1889, 223.3, 233.7, 236.7, 239.4	C67.0-C67.9, D409.0, D430.3, D441.4
Cervix Uteri†	171	180	180	C53
Corpus Uteri†	172	182.0	182.0	C54
Kidney	180	189	189	C64-C66, C68
Other female sites†	173, 174, 176	181, 182.9, 184	179, 181, 182.8, 184	C51, C53, C55, C57.7, C57.8, C57.9,C58
Ovary†	175.0	183.0	183.0	C56
Penis‡	179.0	187.0	187.1,187.2, 187.3, 187.4	C60
Prostate‡	177	185	185	C61
Testis‡	178	186	186	C62

ICD -International Classification of Diseases
† Female sites only
‡ male sites only
§ In ICD-7, bladder benign and unspecified tumours could not be solely identified since they would have been coded under one main category of kidney and other urinary organs- 219 and other genitourinary organs-236 so these categories were not included

Table 5.4 Overall genitourinary subsequent primary neoplasms for PanCareSurFup cohort (n=75,217), Standardised Incidence Ratios, Absolute Excess Risks, adjusted Relative Risks and Relative Excess Risks

	Number of 5-year survivors	Person-years	O/E	SIR (95%CI)	RR (95%CI)	AER (95%CI)	RER (95%CI)
Overall	75,217	1179332.3	277/165.0	1.7 (1.5-1.9)		1.0 (0.8-1.2)	
Gender							
Male	41,075	633240.0	132/84.9	1.6 (1.3-1.8)	1.0 (referent)†	0.7 (0.5-1.2)	1.0 (referent)†
Female	34,142	546092.2	145/80.0	1.8 (1.5-2.1)	1.2 (0.9-1.5)	1.2 (0.8-1.7)	1.5 (0.9-2.7)
$P_{heterogeneity}$				0.20	0.18	0.12	0.10
Attained age							
<20	38,361	449746.9	18/6.0	3.0 (1.9-4.7)	1.0 (referent)†	0.3 (0.1-0.5)	1.0 (referent)†
20-29	25,631	409732.4	69/44.2	1.6 (1.2-2.0)	0.6 (0.4-1.0)	0.6 (0.3-1.2)	3.0 (1.1-8.2)
30-39	8,356	213615.1	77/46.3	1.7 (1.3-2.1)	0.7 (0.4-1.2)	1.4 (0.8-2.5)	11.2 (4.3-29.5)
40-49	2,290	78509.1	46/28.3	1.6 (1.2-2.2)	0.8 (0.5-1.5)	2.3 (1.1-4.8)	39.2 (12.8-119.7)
≥50	579	27728.8	67/40.1	1.7 (1.3-2.1)	1.1 (0.5-2.1)	9.7 (5.3-17.6)	221.7 (53.8-913.6)
P_{trend}				0.34	0.28	<0.001	<0.001
Childhood Cancer							
Leukaemia	20,414	275716.1	26/22.3	1.2 (0.8-1.7)	0.8 (0.5-1.4)	0.1 (0.0-2.0)	0.5 (0.0-6.7)
Hodgkin's disease	6,484	93666.2	20/16.1	1.2 (0.8-1.9)	1.0 (0.6-1.7)	0.4 (0.0-3.9)	0.9 (0.1-6.5)
NHL	3,853	60219.1	17/9.2	1.8 (1.1-3.0)	1.4 (0.8-2.5)	1.3 (0.5-3.6)	3.4 (1.0-11.7)
CNS tumour	14,211	228906.4	47/36.1	1.3 (1.0-1.7)	1.0 (referent)†	0.5 (0.1-1.6)	1.0 (referent)†
Neuroblastoma	3,932	61939.0	11/4.5	2.4 (1.3-4.4)	1.5 (0.8-3.1)	1.0 (0.4-2.9)	3.0 (0.8-11.1)
Retinoblastoma	2,466	57008.8	23/6.6	3.5 (2.3-5.3)	2.4 (1.4-4.2)	2.9 (1.6-5.1)	4.4 (1.3-14.9)
Wilms	5,313	99323.4	29/8.7	3.3 (2.3-4.8)	1.9 (1.2-3.2)	2.0 (1.2-3.4)	3.7 (1.2-11.3)
Bone sarcoma	3,376	53342.6	11/11.3	1.0 (0.5-1.8)	0.8 (0.4-1.5)	0.0 (0.0,.)	0.3 (0.0-16.1)
Soft tissue sarcoma	4,786	83152.5	33/14.1	2.3 (1.7-3.3)	1.8 (1.1-2.7)	2.3 (1.3-4.1)	3.1 (0.9-10.5)
Others	10,382	166058.2	60/36.1	1.7 (1.3-2.1)	1.3 (0.9-2.0)	1.4 (0.8-2.7)	1.9 (0.6-6.6)
$P_{heterogeneity}$				<0.001	<0.01	<0.001	0.01
Country							
Denmark	4,781	77714.4	32/24.0	1.3 (0.9-1.9)	0.8 (0.5-1.2)	1.0 (0.3-4.1)	0.1 (0.0-26.1)
Finland	6,150	103521.6	36/22.1	1.6 (1.2-2.3)	0.9 (0.6-1.4)	1.3 (0.6-3.1)	0.5 (0.1-2.2)
France	3,037	67352.9	29/8.4	3.4 (2.4-5.0)	1.5 (1.0-2.4)	3.1 (1.8-5.1)	1.9 (1.0-3.7)
Hungary	4,873	49939.6	10/3.7	2.7 (1.5-5.1)	1.4 (0.7-2.8)	1.3 (0.5-3.4)	2.0 (0.6-6.4)
Iceland	274	3461.9	0/0.6	0.0 (.,.)	0.0 (0.0,.)	0.0 (0.0,.)	0.0 (0.0,.)
Italy-population-based	10,833	135183.7	13/15.9	0.8 (0.5-1.4)	0.5 (0.3-0.9)	0.0 (0.0,.)	0.3 (0.0-2.3)
Italy-hospital-based	9,136	107960.1	7/7.9	0.9 (0.4-1.9)	0.5 (0.2-1.0)	0.0 (0.0,.)	0.0 (0.0-131134)
Netherlands	6,075	103659.4	25/10.9	2.3 (1.6-3.4)	1.1 (0.7-1.8)	1.4 (0.7-2.7)	1.1 (0.4-2.7)
Sweden	7,710	115387.6	27/18.7	1.4 (1.0-2.1)	0.9 (0.5-1.4)	0.7 (0.2-2.5)	1.3 (0.4-3.4)
Switzerland	4,390	46285.6	5/4.1	1.2 (0.5-2.9)	0.6 (0.3-1.6)	0.2 (0.0-28.3)	0.4 (0.0-7.6)
UK	17,958	368864.8	93/48.6	1.9 (1.6-2.3)	1.0 (referent)†	1.2 (0.8-1.8)	1.0 (referent)†
$P_{heterogeneity}$				<0.001	0.02	<0.001	0.02
Decade of diagnosis							
<1970	8,682	278892.2	121/80.9	1.4 (1.3-1.8)	1.0 (referent)†	1.4 (0.8-2.5)	1.0 (referent)†
1970-1979	14,481	333193.9	86/41.3	2.1 (1.7-2.6)	1.9 (1.3-2.7)	1.3 (0.9-2.0)	4.0 (1.6-9.6)
1980-1989	22,761	363551.0	53/31.2	1.7 (1.3-2.2)	1.8 (1.1-2.8)	0.6 (0.3-1.2)	4.4 (1.4-13.6)
1990-1999	21,784	178297.7	16/10.6	1.5 (0.9-2.5)	1.9 (0.9-3.7)	0.3 (0.0-1.3)	3.3 (0.4-26.7)
≥2000	7,509	25397.5	1/0.9	1.1 (0.2-7.7)	1.2 (0.2-9.5)	0.0 (0.0-3790.0)	0.0 (0.0,.)
P_{trend}				0.53	0.03	<0.01	0.04
Age at diagnosis							
0-4	30,164	495845.6	89/37.3	2.4 (1.9-2.9)	1.0 (referent)†	1.0 (0.7-1.5)	1.0 (referent)†
5-9	17,630	280272.9	58/32.4	1.8 (1.4-2.3)	0.9 (0.7-1.4)	0.9 (0.5-1.6)	0.8 (0.4-1.6)
10-14	16,697	264496.5	73/52.5	1.4 (1.1-1.8)	0.7 (0.5-1.1)	0.8 (0.3-1.8)	0.4 (0.2-1.0)
15-19	10,726	138717.2	57/42.8	1.3 (1.0-1.7)	0.7 (0.4-1.1)	1.0 (0.4-2.9)	0.2 (0.0-0.8)
P_{trend}				<0.001	0.10	0.61	0.01
Follow-up from 5-year Survival							
0-9	52,631	606067.0	51/26.6	1.9 (1.5-2.5)	1.0 (referent)§	0.4 (0.2-0.7)	1.0 (referent)§
10-19	16,114	353523.5	61/46.9	1.3 (1.0-1.7)	0.5 (0.4-0.8)	0.4 (0.1-1.2)	0.7 (0.3-2.2)
20-29	4,981	157034.8	65/41.2	1.6 (1.2-2.0)	0.7 (0.4-1.1)	1.5 (0.8-2.9)	4.2 (1.9-9.3)
30-39	1,296	51932.8	65/31.6	2.1 (1.6-2.6)	1.4 (0.8-2.3)	6.4 (4.0-10.3)	38.4 (14.3-103.0)
≥40	195	10774.2	35/18.5	1.9 (1.4-2.6)	1.3 (0.7-2.4)	15.3 (7.6-30.9)	174.2 (47.6-637.3)
P_{trend}				0.23	0.04	<0.001	<0.001

AER: absolute excess risk, CNS: central nervous system tumour, CI: confidence interval, NHL: Non-Hodgkin Lymphoma, O/E: Observed/Expected, RER: relative excess risks, RR: relative risk, SIR: standardised incidence ratios

† multivariable Poisson model adjusted for sex, attained age, childhood cancer diagnosis, country of diagnosis, decade of diagnosis and age at diagnosis

§ multivariable Poisson model adjusted for sex, follow-up from 5-year survival, childhood cancer diagnosis, country of diagnosis, decade of diagnosis and age at diagnosis

Figure 5.1 Cumulative risk of developing a genitourinary subsequent primary neoplasm and corresponding expected risk.

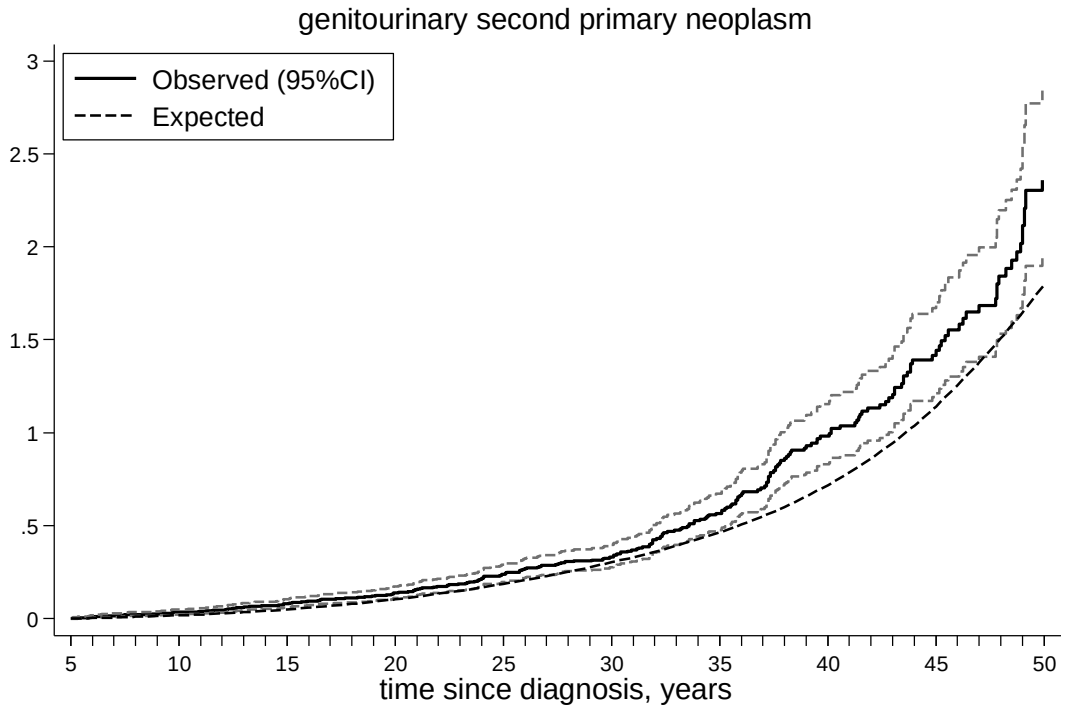


Figure 5.2 Cumulative risk of developing a genitourinary subsequent primary neoplasm of any type by childhood cancer diagnosis

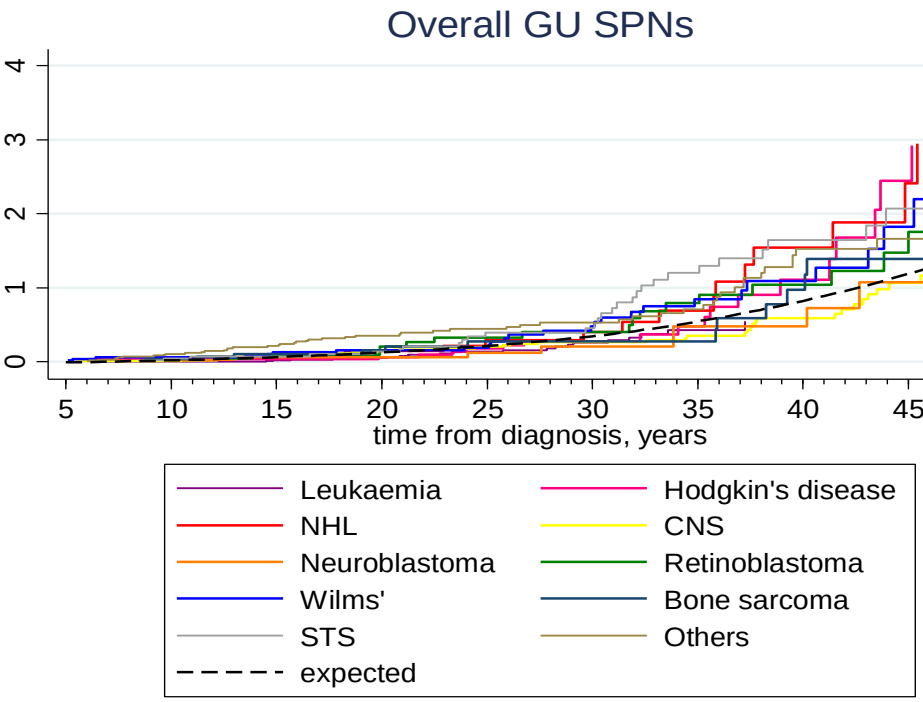


Figure 5.3 Cumulative risk of developing a genitourinary subsequent primary neoplasm of any type by country of diagnosis

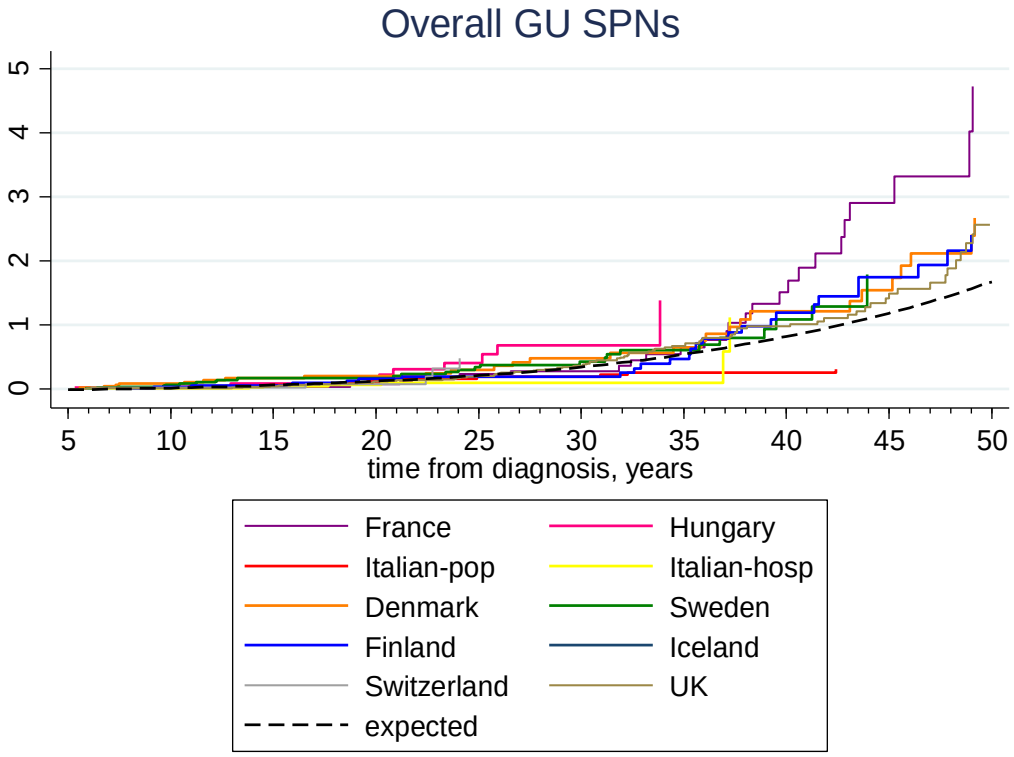


Table 5.5 Frequency of Genitourinary Site Subsequent Primary Neoplasms by First Primary Neoplasm Diagnosis

FPN diagnosis	Site of Genitourinary Subsequent Primary Neoplasm									
	Kidney	Bladder†	Testis	Ovary	Corpus uteri	Cervix uteri	Prostate	Other female	Penis	Total (%)
Leukaemia	5	8	5	2	1	4	1	0	0	**26 (9.4)**
Hodgkin's Disease	7	2	1	3	0	2	1	3	1	**20 (7.2)**
NHL	5	4	2	1	2	0	2	1	0	**17 (6.1)**
CNS	5	4	8	15	5	4	5	1	0	**47 (17.0)**
Neuroblastoma	5	2	1	1	0	1	1	0	0	**11 (4.0)**
Retinoblastoma	0	9	3	2	6	1	1	1	0	**23 (8.3)**
Wilms'	16	2	2	0	5	3	0	1	0	**29 (10.5)**
Bone Sarcoma	1	2	1	1	1	3	2	0	0	**11 (4.0)**
STS	5	5	3	6	2	2	6	4	0	**33 (11.9)**
Others	21	6	13	6	7	3	2	3	0	**60 (21.7)**
Total (%)	**70 (25.3)**	**44 (15.9)**	**38 (13.7)**	**37 (13.4)**	**29 (10.5)**	**23 (8.3)**	**21 (7.6)**	**14 (5.1)**	**1 (0.4)**	**277 (100)**

CNS: central nervous system; FPN: first primary neoplasm NHL: Non-Hodgkin lymphoma; STS: soft tissue sarcoma
† malignant bladder only as general population rates are based on malignant codes

Table 5.6 Standardised incidence ratios and absolute excess risks of genitourinary subsequent primary neoplasms by site.

SPN Site	O/E	SIR (95%CI)	AER (95%CI)
Kidney	70/13.4	5.2 (4.1-6.6)	0.5 (0.4-0.6)
Bladder	44/12.0	3.7 (2.7-4.9)	0.3 (0.2-0.4)
Other female sites	14/4.1	3.4 (2.0-5.7)	0.1 (0.0-0.1)
Corpus uteri	29/10.7	2.7 (1.9-3.9)	0.1 (0.1-0.2)
Ovary	37/22.0	1.7 (1.2-2.3)	0.1 (0.0-0.2)
Prostate	21/16.4	1.3 (0.8-2.0)	0.0 (0.0-0.2)
Penis	1/1.1	0.9 (0.1-6.3)	0
Testis	38/50.2	0.8 (0.6-1.0)	0
Cervix uteri	23/35.0	0.6 (0.4-1.0)	0

AER: absolute excess risk, CI: confidence interval, O/E: observed/expected; SIR: standardised incidence ratio, SPN: subsequent primary neoplasm

Table 5.7 Standardised incidence ratios and absolute excess risks for bladder, kidney, ovary and testis subsequent primary neoplasms

	Bladder SPN			Kidney SPN			Ovary SPN			Testis SPN		
Explanatory factor	**O/E**	**SIR (95%CI)**	**AER (95%CI)**	**O/E**	**SIR (95%CI)**	**AER (95%CI)**	**O/E**	**SIR (95%CI)**	**AER (95%CI)**	**O/E**	**SIR (95%CI)**	**AER (95%CI)**
Sex												
Male	30/8.8	3.4 (2.4-4.9)	0.3 (0.2-0.6)	42/8.4	5.0 (3.7-6.7)	0.5 (0.4-0.8)	NA	NA	NA	38/50.2	0.8 (0.6-1.0)	0
Female	14/3.1	4.5 (2.6-7.5)	0.2 (0.1-0.4)	28/5.0	5.6 (3.9-8.2)	0.4 (0.3-0.7)	37/22.0	1.7 (1.2-2.3)	0.1 (0.0-0.2)	NA	NA	NA
$P_{heterogeneity}$		0.40	0.22		0.62	0.4						
Childhood Cancer												
Leukaemia	8/0.7	11.3 (5.7-22.6)	0.3 (0.1-0.6)	5/1.3	3.8 (1.6-9.2)	0.1 (0.0-0.4)	2/3.0	0.7 (0.2-2.6)	0	5/10.0	0.5 (0.2-1.2)	0
Hodgkin's Disease	2/1.2	1.7 (0.4-7.0)	0.1 (0.0-2.3)	7/1.3	5.3 (2.5-11.2)	0.6 (0.2-1.5)	3/1.6	1.9 (0.6-5.8)	0.1 (0.0-1.7)	1/6.0	0.2 (0.0-1.2)	0
NHL	4/0.8	5.3 (2.0-14.1)	0.5 (0.2-1.8)	5/0.8	6.0 (2.5-14.5)	0.7 (0.2-2.0)	1/0.8	1.2 (0.2-8.6)	0	2/3.7	0.5 (0.1-2.1)	0
CNS	4/2.9	1.4 (0.5-3.7)	0.0 (0.0-1.8)	5/3.1	1.6 (0.7-3.9)	0.1 (0.0-0.8)	15/4.8	3.1 (1.9-5.2)	0.4 (0.2-0.9)	8/10.0	0.8 (0.4-1.6)	0
Neuroblastoma	2/0.2	10.4 (2.6-41.6)	0.3 (0.1-1.4)	5/0.4	14.4 (6.0-34.5)	0.8 (0.3-1.9)	1/0.7	1.5 (0.2-10.5)	0.1 (0.0-22.8)	1/1.6	0.6 (0.1-4.4)	0
Retinoblastoma	9/0.5	19.7 (10.2-37.8)	1.5 (0.8-3.0)	0/0.6	0.0 (.,.)	0.0 (0.0,.)	2/0.9	2.1 (0.5-8.6)	0.2 (0.0-2.5)	3/1.9	1.6 (0.5-5.0)	0.2 (0.0-4.0)
Wilms'	2/0.4	5.0 (1.3-20.1)	0.2 (0.0-0.9)	16/0.6	25.7 (15.7-41.9)	1.5 (0.9-2.6)	0/1.3	0	0	2/3.2	0.6 (0.2-2.5)	0
Bone Sarcoma	2/1.0	2.0 (0.5-8.0)	0.2 (0.0-3.0)	1/1.0	1.0 (0.1-6.8)	0.0 (0.0,.)	1/1.4	0	0	1/2.8	0.4 (0.1-2.5)	0
STS	5/1.3	3.8 (1.6-9.2)	0.4 (0.1-1.5)	5/1.3	3.8 (1.6-9.2)	0.4 (0.1-1.4)	6/1.8	0.7 (0.1-5.1)	0.5 (0.2-1.6)	3/3.7	0.8 (0.3-2.5)	0
Others	6/3.1	1.9 (0.9-4.3)	0.2 (0.0-0.9)	21/3.0	7.0 (4.5-10.7)	1.1 (0.7-1.8)	6/5.7	1.1 (0.5-2.3)	0	12/7.3	1.6 (0.9-2.9)	0.3 (0.1-1.2)
$P_{heterogeneity}$		<0.001	0.02		<0.001	<0.001		0.08	0.07		0.13	0.98
Attained Age												
<20	1/0.2	6.1 (0.9-43.2)	0.0 (0.0-0.2)	9/0.7	12.8 (6.7-24.6)	0.2 (0.1-0.4)	5/1.5	3.4 (1.4-8.1)	0.1 (0.0-0.3)	2/3.4	0.6 (0.1-2.4)	0
20-29	9/1.1	8.3 (4.3-16.0)	0.2 (0.1-0.4)	15/1.2	13.1 (7.9-21.7)	0.3 (0.2-0.6)	12/4.7	2.5 (1.4-4.5)	0.2 (0.1-0.5)	24/25.4	0.9 (0.6-1.4)	0
30-39	19/2.0	9.4 (6.0-14.8)	0.8 (0.5-1.3)	17/2.6	6.5 (4.1-10.5)	0.7 (0.4-1.2)	5/5.4	0.9 (0.4-2.2)	0.0 (0.0,.)	10/16.9	0.6 (0.3-1.1)	0
40-49	7/3.0	2.4 (1.1-5.0)	0.5 (0.1-1.9)	14/3.9	3.6 (2.1-6.0)	1.3 (0.6-2.7)	5/5.5	0.9 (0.4-2.2)	0.0 (0.0,.)	1/3.9	0.3 (0.0-1.8)	0
≥50	8/5.8	1.4 (0.7-2.8)	0.8 (0.1-9.6)	15/5.0	3.0 (1.8-4.9)	3.6 (1.7-7.7)	10/5.0	2.0 (1.1-3.7)	1.8 (0.5-6.2)	1/0.6	1.8 (0.3-12.9)	0.2 (0.0-12.6)
P_{trend}		<0.001	<0.001	<0.001	<0.001	<0.001		0.13	0.65		0.50	0.86

AER: absolute excess risks, CNS: central nervous system, NA: not applicable, NHL: Non-Hodgkin lymphoma, O/E: observed/expected, SIR: standardised incidence ratio, STS: soft tissue sarcoma

Figure 5.4 Cumulative risk of developing a kidney subsequent primary neoplasm

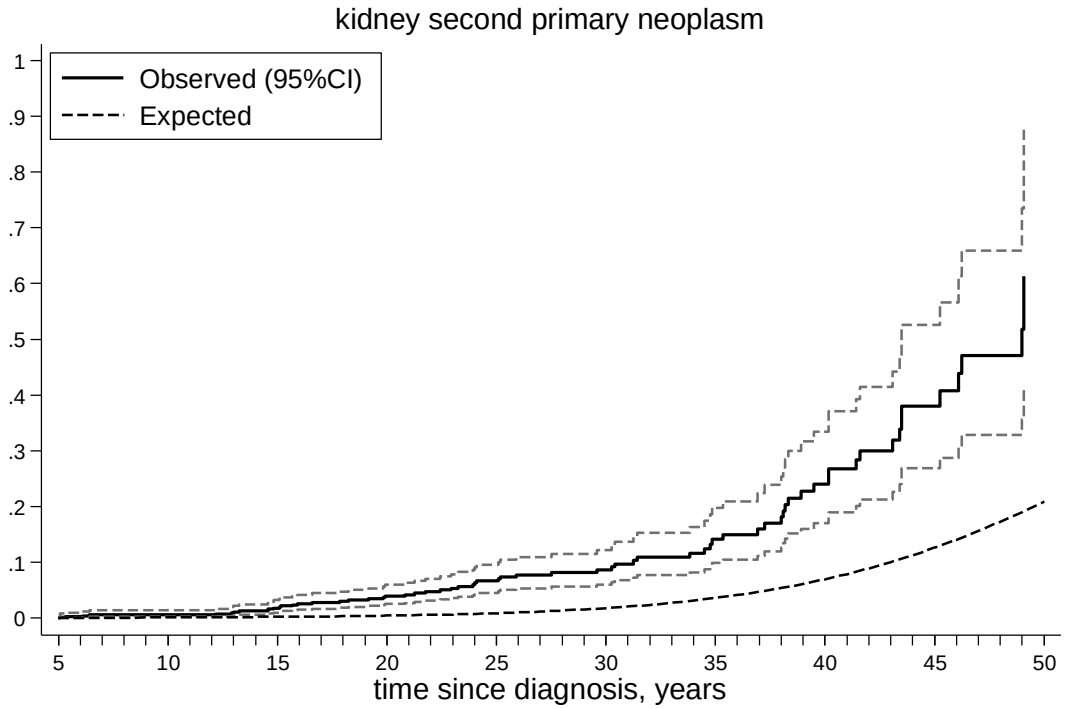
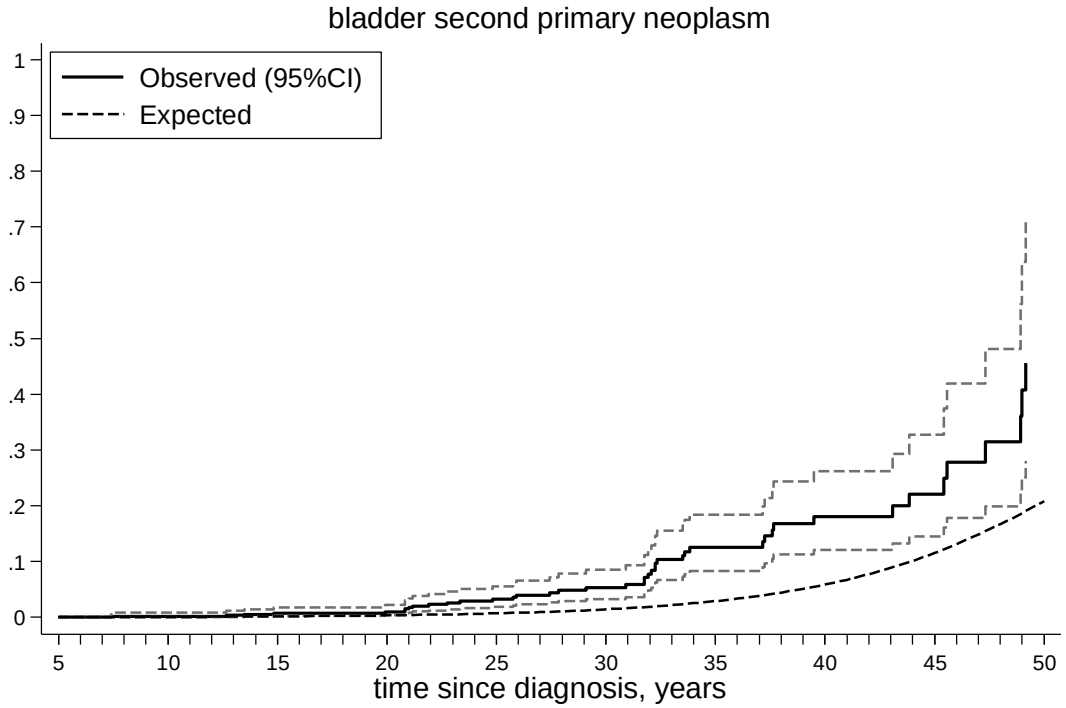


Figure 5.5 Cumulative risk of developing a bladder subsequent primary neoplasm



CHAPTER 6 GENERAL DISCUSSION AND CONCLUSIONS

6.1 Principal findings

Chapter Two investigated which survivors in the BCCSS were on regular long-term hospital follow-up. The NCSI has proposed substantial changes to clinical follow-up practices within the NHS for the future. Changes proposed are a move away from a one-size fits all model of follow-up towards risk stratification, whereby the level of care to be offered corresponds to the anticipated level of risk of serious adverse health outcomes. Survivors were assigned to proposed NCSI Levels of care (risk stratification levels developed by the BCCSS in collaboration with NCSI clinicians and based on cancer type and treatment received). Among LEVEL 3 survivors of non-leukaemic cancer only 31% were on regular hospital follow-up, despite the NCSI recommendation for all LEVEL 3 survivors to be on regular hospital multi-disciplinary team review, furthermore this percentage declined from 57% to 16% among survivors aged under 20 years to survivors aged at least 50 years, respectively. Among LEVEL 1 survivors of non-leukaemia cancers 12% were on regular hospital follow-up, whilst the NCSI recommendation for all LEVEL 1 survivors is self-care with support. GPs returns indicated that 74% (9595/12978) were willing to discuss survivorship issues with survivors. Consideration needs to be given to the potential recall of both NCSI LEVEL 3 survivors who are not on regular hospital follow-up for possible establishment of such follow-up, and NCSI LEVEL 1 survivors who are on such follow-up for possible discharge to self-care with support.

Chapter Three explored which groups of survivors of CNS tumours within the BCCSS were at excess risk of adverse health and social outcomes using record-linkage (for causes of death and incident SPNs) and the BCCSS study questionnaire data (for non-fatal, non-neoplastic outcomes) by comparing risks to that expected from the general population. Between 30 and 50 years from diagnosis the principal causes of death accounting for most of the total excess

deaths observed were: after craniopharyngioma, recurrence (28%) and circulatory (35%); after medulloblastoma, recurrence (20%) and SPN (48%); after astrocytoma, recurrence (35%), SPN (13%) and respiratory (13%). Consequently, CNS subtype was a strong risk stratification factor, as was cranial/craniospinal radiotherapy in that, of the total excess number of deaths observed beyond 30 years from diagnosis among those exposed (unexposed) to radiotherapy 21% (3%) and 11% (0%) were attributable to SPN and stroke respectively. The cumulative risks of developing a meningioma by 35 years from diagnosis among those exposed (unexposed) to radiotherapy were 3.9% (0.6%). Educational attainment and marriage showed greater deficits among those CNS tumour survivors who had received cranial/craniospinal irradiation. CNS subtype and cranial irradiation provide strong risk stratification factors which may be used in long-term follow-up clinics to powerfully discriminate between groups of survivors in terms of anticipated risk of serious adverse health outcomes.

Chapter Four demonstrated through electronic record linkage of the BCCSS cohort with Hospital Episode Statistics that overall, 299 survivors were hospitalised for a cerebrovascular condition compared to 59 expected (SHR=5.1, 95%CI:4.5-5.7) with survivors of a CNS tumour (SHR=11.9, 95%CI:10.3-13.7, AER=8.5, 95%CI:3.9-18.3) and leukaemia (SHR=5.6, 95%CI:4.2-7.4, AER=2.3, 95%CI:1.0-5.0) at the greatest excess risk. Of the specific cerebrovascular conditions, the greatest observed hospitalisations among survivors were for cerebral haemorrhage (SHR=8.1, 95%CI:6.7-9.8) and ischaemic stroke (SHR=5.2, 95%CI:4.3-6.2), with CNS tumour survivors at particular increased risk. Previous treatment with cranial irradiation was associated with increased risk of being hospitalised for a cerebrovascular condition over that expected (SHR=15.6, 95%CI:13.0-18.9). In absolute terms this equated to 58 additional hospitalisations per 10,000 person-years. Hospitalisation

due to a cerebrovascular condition and more specifically hospitalisations due to cerebral haemorrhage and ischaemic stroke is greatest in survivors who were initially diagnosed with a CNS tumour or leukaemia. Cranial irradiation is a strong risk factor associated with survivors being hospitalised for cerebrovascular complications. A risk-stratified approach to clinical follow-up, would ensure survivors at highest risk of cerebrovascular complications undergo surveillance.

Chapter Five, the largest ever cohort study undertaken to comprehensively investigate the risk of genitourinary primary cancers subsequent to childhood cancer survivors throughout Europe using the PanCareSurFup cohort found that after a mean follow-up time of 20.7 years, 277 (0.37%) genitourinary SPNs were diagnosed among 75,217 survivors of childhood cancer. The most commonly observed genitourinary SPNs were of the kidney (n=70), bladder (n=44) and testis (n=38). Overall, survivors were twice as likely to develop a genitourinary SPN of any type than expected (SIR=1.7, 95%CI:1.5-1.9, AER=1.0, 95%CI:0.8-1.2). Survivors of retinoblastoma (SIR=3.5, 95%CI:2.3-5.3) and Wilms' tumour (SIR=3.3, 95%CI:2.3-4.8) were at the greatest risk of developing any genitourinary SPN. Overall, survivors had a 5-fold expected risk of developing a kidney SPN (SIR=5.2, 95%CI:4.1-6.6) and a 4-fold expected risk of developing a bladder SPN (SIR=3.7, 95%CI:2.7-4.9). Male survivors were not at a significantly increased risk of developing a testicular SPN (SIR=0.8, 95%CI:0.6-1.0). Survivors of retinoblastoma were at increased risk of developing bladder SPNs while Wilms' tumours survivors were at increased risk of developing kidney SPNs. It is important that health professionals involved in the long-term follow-up care of childhood cancer survivors are aware of the excess risks of genitourinary SPNs as survivors become older so they may provide information accordingly and counsel survivors in relation to early symptoms.

6.2 Methodological Considerations

Two principal advantages of using the BCCSS are its large-scale and its population-based study design, this provides reliable and unbiased risk estimates with regards to a whole spectrum of adverse outcomes that have been studied. The BCCSS was ascertained through the National Registry for Childhood Tumours which has a high level of completeness of ascertainment ~99% (270). Since all childhood cancer survivors are included, there is unlikely to be selection bias present in the population-based BCCSS that is inherent in hospital-based studies. In studies such as the CCSS, childhood cancer survivors are ascertained through a limited number (twenty-five) of research orientated treatment centres, therefore the survivors ascertained are unlikely to be representative of all childhood cancer survivors in North America. Furthermore, as the CCSS restrict their inclusion criteria to specific diagnoses (33), some childhood cancer survivors are inevitably excluded from their study.

As a result of including survivors of childhood cancer diagnosed since 1940, the BCCSS has a much longer follow-up period compared with studies such as the CCSS (33), SCCSS (32) and DCOG LATER study (31). Thus it is possible to investigate late effects among survivors many years after their original childhood cancer diagnosis. Extension of the BCCSS cohort from 1st January 1992 to 31st December 2006 enables comparisons between survivors diagnosed and treated decades ago with survivors diagnosed and treated more recently.

Further advantages of the BCCSS include its linkage with HSCIC (formerly known as NHS Central Registers) and the provision of key information through flagging with respect to deaths and second cancers. Every survivor's vital status is provided by linkage with the national death registration system while notification of a survivor developing a SPN is through the national cancer registration system. For survivors who are alive, current registration with a general practice can be identified through their NHS status. Thus once survivors in the BCCSS cohort have been flagged with HSCIC, there is an efficient way to

trace these individuals minimising loss-to-follow-up. Tracing individuals in hospital-based studies is often more difficult, particularly as survivors move locations and hospital records are not updated with key information (271).

A study questionnaire, based on that used in the CCSS, was developed and distributed by post to survivors in the BCCSS via their GP. This study questionnaire was used to ascertain the majority of outcomes investigated in Chapter Three. In any self-reported questionnaire, response bias needs to be taken into consideration, which is the systematic error caused by differences in the outcome being measured between respondents and non-respondents (272). The overall response rate for the questionnaire was 70.7%, which is high in research using questionnaires, particularly those sent by post (273). The distribution of survivor characteristics did not differ substantially between responders and non-responders to the questionnaire, which provides some reassurance in relation to potential response bias (30).

The disadvantage of the BCCSS is its lack of detailed treatment information for each survivor within the cohort. Some treatment information is available for cohort members with respect to surgery, radiotherapy and chemotherapy which has been recorded discretely as yes, no or no record for each treatment type. With a population-based cohort of 34,489 individuals, it would be a vast undertaking to locate all the medical records of survivors across the UK as well as to collect detailed patient notes in relation to any therapy given during the course of cancer treatment for each survivor. One way of addressing this limitation is to conduct nested case-control studies. The cases and controls are selected from the underlying cohort thus minimising selection bias as the cases and controls are selected from the same cohort (271). Various outcomes could be investigated and one would only have to gather treatment exposure on cases and controls as opposed to the entire cohort. The efficiency of the use of

nested case-control studies has been acknowledged when the assessment of exposure is resource-intensive such as radiation dosimetry (271).

The advantages of using Hospital Episode Statistics (HES) to ascertain data with respect to hospitalisations are its large size and population-based coverage across England which considered together provide robust evidence. The BCCSS questionnaire has been used to ascertain various non-fatal and non-neoplastic adverse health and social outcomes up until now, however the investigation of cerebrovascular disease among childhood cancer survivors in Chapter Four demonstrates another method of ascertaining such information. This methodology is less resource intensive than sending out questionnaires and is based on medical diagnoses and therefore likely to be valid than outcomes self-reported in a questionnaire (235). Hospital record linkage also removes the issue of potential recall bias, which is an important consideration of self-reported questionnaires. Linking the BCCSS cohort with HES minimises loss-to-follow-up in ascertaining outcomes among survivors as they are both population-based sources. The disadvantage of HES is that it is for England only, equivalent hospital databases are available for both Scotland and Wales and permission is currently being sought to link the BCCSS cohort with these databases.

There are several advantages of establishing the PanCareSurFup cohort, firstly it is the largest ever cohort of childhood cancer survivors in the world. Secondly, the cohort possesses a long-period of follow-up as it includes the UK and Nordic countries with diagnoses going back to the 1940s. Finally, as PanCareSurFup is an international project, there is collaboration with experts in the field to work towards providing the best evidence possible for survivors of childhood cancer. Due to the long period of follow-up available, survivors in this cohort are reaching ages where common diseases occur in mature adulthood in the general population (including cancer, cardiovascular, pulmonary and diabetes). This enables a much more

informative investigation of such diseases compared with the risk expected from the general population. In previous research, it has not been possible to quantify the excess risks of site-specific genitourinary SPNs comprehensively among childhood cancer survivors as a small number of SPNs have been ascertained in previous cohorts (59, 60, 63, 64). Only now with a collaborative international study with cases being pooled may the risk of specific SPNs be investigated satisfactorily. The age at cancer diagnosis eligibility range for the BCCSS was to include individuals diagnosed with cancer between the ages of 0 and 14 years. For the PanCareSurFup cohort, the age at cancer diagnosis eligibility range was between 0 and 19 years since some countries contributing to this cohort had a wider age at cancer diagnosis eligibility range. The ICCC was used to classify childhood cancers in the PanCareSurFup cohort as the third volume includes the age range of 0 to 19 years (12). Limitations in relation to this international cohort include the lack of treatment information which is being addressed through nested case-control studies. Standardising data collection has not been without its difficulties. For instance, Slovenia and Norway mainly use the ICD (a site-based code) to classify their childhood cancers which limits suitable conversions into certain aggregated diagnostic groups using the ICCC which requires both site and type information. This is being addressed with data providers and although the current cohort excludes these countries in the SPN analysis that has been conducted, there is potential to address these issues in the future.

6.3 Implications on Guidelines

This thesis has highlighted that a risk stratification tool developed by the BCCSS in collaboration with the NCSI may be used to determine the level of clinical follow-up care survivors should receive depending on their risk of serious adverse health outcomes. Findings from Chapter Two demonstrate which survivors could possibly be discharged from hospital-follow-up due to their low risk of serious adverse health outcomes and which survivors should

probably be on hospital follow-up and may need possible recall to the NHS. Current SIGN guidelines propose possible levels of follow-up for survivors based on therapy given to survivors and their cancer types (17). These levels are broadly similar to those proposed by the BCCSS/NCSI. The risk stratification tool proposed by the BCCSS/NCSI is evidence-based in that the risk of the total burden of disease from all adverse health outcomes has been quantified for each level. Previous studies have proposed levels of follow-up based on risk-stratification but these have been small-scale studies in hospital-based settings (42, 274, 275). Such studies may be prone to selection bias in their inclusion of participating survivors. A more recent study based in a single institution in Scotland proposed risk-stratification levels but these are based on a younger cohort than the BCCSS (276). Since the cumulative risk of many chronic conditions increase substantially with increasing time from diagnosis (49), findings from younger cohorts are inevitably rather limited. Thus in proposing levels of follow-up using risk stratification, one needs to consider the risks that mature survivors will be facing as well as those faced by younger survivors. In suggesting new levels of clinical follow-up, it will also be important to ensure survivors are fully informed about their childhood cancer diagnosis and the treatment they received as they may have been of ages where they were not involved in this exchange of information. Knowledge deficits among childhood cancer survivors regarding their cancer diagnosis and previous treatment have been reported (277).

CNS tumour survivors are a heterogeneous group and this thesis demonstrates that CNS subtype and cranial/craniospinal radiation are strong risk-stratification factors in determining the risks reported for a spectrum of adverse health and social outcomes. The current SIGN guidelines state that "many studies lack comparison groups" with regards to psychosocial issues (17). Comparison groups outside of the childhood cancer survivor population are

essential to quantify the excess risk of an outcome of interest experienced by survivors (271). A strength of the findings from Chapter Three are that all comparisons of psychosocial outcomes have been made with the general population thus the estimated excess risk among childhood cancer survivors can be compared to those individuals who did not have a childhood cancer but of a similar age and sex as the survivors. CNS tumour survivors were less likely to demonstrate harmful health behaviours such as smoking regularly and drinking alcohol compared to the general population. There are however survivors that smoke regularly, consume alcohol and have increased risks of BMI, thus health promotion advice will be ever more important as a preventative measure for many chronic diseases. Counselling survivors about their health risks will continue to be an important goal in empowering survivors to make informed lifestyle choices (17).

The importance of replicating findings across different study populations has been stressed in scientific research quantifying risk (151). The study in Chapter Four demonstrated that sub-groups of survivors at high risk of hospitalisations due to cerebrovascular disease were CNS tumours and leukaemia. These findings were in agreement with another large population-based study investigating the same outcome (71). This can only strengthen the evidence-base with respect to this adverse health outcome. The effect of cranial irradiation in the risk of survivors being hospitalised due to cerebrovascular disease is notable in this study. This may change as treatment protocols evolve over time but how this may impact on the vasculature of the brain and risk of cerebrovascular disease is unknown. It is suggested that survivors who have received cranial irradiation require closer monitoring with regards to cerebrovascular disease. Current CCLG and SIGN guidelines (17, 164) lack recommendations in the areas of cerebrovascular disease yet American childhood cancer survivorship guidelines recommend annual neurological examinations for those survivors who have received ≥18 Gy to specified

fields for monitoring of cerebrovascular disease (121). This highlights the need to harmonise guidelines, which is the remit of the International Guideline Harmonisation Group, founded in 2010 (170).

The overall risk of SPNs is well documented in guidelines (17, 121). However the risks of genitourinary SPNs have not been well documented in these guidelines, possibly as there have been few studies with adequate statistical power to investigate the excess risks of such cancers in survivors of childhood cancer. This highlights the need for more evidence. The study in Chapter Five demonstrated that certain groups of survivors are at increased risk of specific types of genitourinary subsequent primary cancers; Wilms' tumour survivors were at increased risk of kidney cancer and retinoblastoma survivors were at increased risk of bladder cancer. SIGN guidelines recommend GPs should be aware of patterns of presentation for SPNs (17). This is ever more important with symptoms such as haematuria which may be indicated as a sign of bladder cancer. Thus patients need to be counselled to recognise early symptoms and seek health advice as appropriate. Providing survivors with summaries of the cancer treatment they received in childhood will equip them with information they may need for the future particularly if the adverse late effects they could experience are many decades after their original cancer diagnosis as is the case with some of the genitourinary cancers.

6.4 Future Research

As the BCCSS cohort has been linked with HES, there is the possibility of ascertaining many more non-fatal non-neoplastic adverse health and social outcomes. HES only records data for hospitals within England therefore there are plans to link the BCCSS cohort with equivalent national databases in Wales (Patient Episode Database for Wales) (278) and Scotland (Information Service Division linked database for Scotland) (279) so coverage across the UK is maximised. There is also the potential to link the BCCSS cohort with other electronic

health record databases such as the Myocardial Ischaemia National Audit Project (MINAP) (280) which would enable further investigation of cerebrovascular disease and modifiable risk-factors such as smoking status, diabetes, hypertension, hypercholesterolaemia and increased BMI. This method of linkage would increase completeness and provide further diagnostic validity to ascertained events.

Risk estimates of childhood cancer survivors developing genitourinary SPNs using the PCSF cohort were reported in Chapter Five. However a limitation in reporting these risk estimates was the lack of exposure information to assess the effect of treatment in the risk of survivors developing these SPNs. As mentioned previously, it will be possible to address this limitation in nested case-control studies that are being conducted as part of the PanCareSurFup project. Selection bias is minimised as the cases and controls will be selected from the underlying PanCareSurFup cohort. Data providers are in the process of collecting comprehensive treatment information relating to radiotherapy and chemotherapy for cases and controls in these nested case-control studies. Multiple exposures can be addressed in the outcome of childhood cancer survivors developing genitourinary SPNs on a scale that is unprecedented in terms of size of case-control studies. International collaboration is advantageous for investigating rare adverse outcomes such as site-specific genitourinary SPNs among childhood cancer survivors as the BCCSS alone would not have enough statistical power to conduct case-control studies but pooling cases with other countries overcomes this limitation.

6.5 General Conclusions

A retrospectively ascertained cohort such as the BCCSS is invaluable in providing empirical risk evidence in relation to a spectrum of adverse health and social outcomes. This thesis demonstrates that reliable and unbiased evidence can be provided from both the original BCCSS cohort, the recently extended BCCSS cohort and working collaboratively with

international partners in forming a European cohort. Findings from this thesis provides evidence to inform changes to the long-term follow-up practices of childhood cancer survivors in the UK; for the first time, follow-up has been approached in an evidence-based manner using risk stratification levels. At a time where resources are limited, the current stance of providing hospital-based multidisciplinary care will not be feasible for all survivors and there is the possibility of some survivors receiving less intensive levels of care. CNS tumour survivors and their risks of adverse outcomes differ by CNS sub-type and treatment with cranial irradiation. It will be important to consider these factors in providing advice regarding late effects and survivorship issues. Overall, childhood cancer survivors are at increased risk of hospitalisations due to cerebrovascular disease compared to the general population, specifically cerebral haemorrhage and ischaemic stroke. Survivor groups at particular increased risk of hospitalisation due to cerebrovascular disease were CNS tumours and leukaemia. CNS tumour survivors who had been treated with cranial irradiation were at an even greater risk of hospitalisation due to cerebrovascular disease. Survivors of Wilms' tumour and retinoblastoma were at the greatest risk of developing any genitourinary SPN; Wilms' tumour survivors were at particular increased risk of developing kidney SPNs and retinoblastoma survivors were at particular increased risk of bladder SPNs. It is important that health professionals involved in the long-term follow-up care of childhood cancer survivors are aware of the excess risks of genitourinary SPNs as survivors become older so they may provide information accordingly and counsel survivors in relation to early symptoms.

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CHAPTER 8 APPENDIX

8.1 International Classification of Childhood Cancer, Third Edition. Steliarova-Foucher et al, Cancer, 2005; 103 (7): 1457-1467.

TABLE 1
International Classification of Childhood Cancer, Third Edition: Main Classification Table

	ICD-O-3 code(s)[10]	
Diagnostic group	**Morphology**	**Topography**
I. Leukemias, myeloproliferative diseases, and myelodysplastic diseases		
a. Lymphoid leukemias	9820, 9823, 9826, 9827, 9831–9837, 9940, 9948	
b. Acute myeloid leukemias	9840, 9861, 9866, 9867, 9870–9874, 9891, 9895–9897, 9910, 9920, 9931	
c. Chronic myeloproliferative diseases	9863, 9875, 9876, 9950, 9960–9964	
d. Myelodysplastic syndrome and other myeloproliferative diseases	9945, 9946, 9975, 9980, 9982–9987, 9989	
e. Unspecified and other specified leukemias	9800, 9801, 9805, 9860, 9930	
II. Lymphomas and reticuloendothelial neoplasms		
a. Hodgkin lymphomas	9650–9655, 9659, 9661–9665, 9667	
b. Non-Hodgkin lymphomas (except Burkitt lymphoma)	9591, 9670, 9671, 9673, 9675, 9678–9680, 9684, 9689–9691, 9695, 9698–9702, 9705, 9708, 9709, 9714, 9716–9719, 9727–9729, 9731–9734, 9760–9762, 9764–9769, 9970	
c. Burkitt lymphoma	9687	
d. Miscellaneous lymphoreticular neoplasms	9740–9742, 9750, 9754–9758	
e. Unspecified lymphomas	9590, 9596	
III. CNS and miscellaneous intracranial and intraspinal neoplasms		
a. Ependymomas and choroid plexus tumor	9383, 9390–9394[a]	
b. Astrocytomas	9380[a]	C72.3
	9384, 9400–9411, 9420, 9421–9424, 9440–9442[a]	
c. Intracranial and intraspinal embryonal tumors	9470–9474, 9480, 9508[a]	
	9501–9504[a]	C70.0–C72.9
d. Other gliomas	9380[a]	C70.0–C72.2, C72.4–C72.9, C75.1, C75.3
	9381, 9382, 9430, 9444, 9450, 9451, 9460[a]	
e. Other specified intracranial and intraspinal neoplasms	8270–8281, 8300, 9350–9352, 9360–9362, 9412, 9413, 9492, 9493, 9505–9507, 9530–9539, 9582[a]	
f. Unspecified intracranial and intraspinal neoplasms	8000–8005[a]	C70.0–C72.9, C75.1–C75.3
IV. Neuroblastoma and other peripheral nervous cell tumors		
a. Neuroblastoma and ganglioneuroblastoma	9490, 9500	
b. Other peripheral nervous cell tumors	8680–8683, 8690–8693, 8700, 9520–9523	
	9501–9504	C00.0–C69.9, C73.9–C76.8, C80.9
V. Retinoblastoma	9510–9514	
VI. Renal tumors		
a. Nephroblastoma and other nonepithelial renal tumors	8959, 8960, 8964–8967	
	8963, 9364	C64.9
b. Renal carcinomas	8010–8041, 8050–8075, 8082, 8120–8122, 8130–8141, 8143, 8155, 8190–8201, 8210, 8211, 8221–8231, 8240, 8241, 8244–8246, 8260–8263, 8290, 8310, 8320, 8323, 8401, 8430, 8440, 8480–8490, 8504, 8510, 8550, 8560–8576	C64.9
	8311, 8312, 8316–8319, 8361	
c. Unspecified malignant renal tumors	8000–8005	C64.9
VII. Hepatic tumors		
a. Hepatoblastoma	8970	
b. Hepatic carcinomas	8010–8041, 8050–8075, 8082, 8120–8122, 8140, 8141, 8143, 8155, 8190–8201, 8210, 8211, 8230, 8231, 8240, 8241, 8244–8246, 8260–8264, 8310, 8320, 8323, 8401, 8430, 8440, 8480–8490, 8504, 8510, 8550, 8560–8576	C22.0, C22.1
	8160–8180	
c. Unspecified malignant hepatic tumors	8000–8005	C22.0, C22.1

(continued)

TABLE 1
(continued)

Diagnostic group	ICD-O-3 code(s)[10] Morphology	Topography
VIII. Malignant bone tumors		
a. Osteosarcomas	9180–9187, 9191–9195, 9200	C40.0–C41.9, C76.0–C76.8, C80.9
b. Chondrosarcomas	9210, 9220, 9240	C40.0–C41.9, C76.0–C76.8, C80.9
	9221, 9230, 9241–9243	
c. Ewing tumor and related sarcomas of bone	9260	C40.0–C41.9, C76.0–C76.8, C80.9
	9363–9365	C40.0–C41.9
d. Other specified malignant bone tumors	8810, 8811, 8823, 8830	C40.0–C41.9
	8812, 9250, 9261, 9262, 9270–9275, 9280–9282, 9290, 9300–9302, 9310–9312, 9320–9322, 9330, 9340–9342, 9370–9372	
e. Unspecified malignant bone tumors	8000–8005, 8800, 8801, 8803–8805	C40.0–C41.9
IX. Soft tissue and other extraosseous sarcomas		
a. Rhabdomyosarcomas	8900–8905, 8910, 8912, 8920, 8991	
b. Fibrosarcomas, peripheral nerve sheath tumors, and other fibrous neoplasms	8810, 8811, 8813–8815, 8821, 8823, 8834–8835	C00.0–C39.9, C44.0–C76.8, C80.9
	8820, 8822, 8824–8827, 9150, 9160, 9491, 9540–9571, 9580	
c. Kaposi sarcoma	9140	
d. Other specified soft tissue sarcomas	8587, 8710–8713, 8806, 8831–8833, 8836, 8840–8842, 8850–8858, 8860–8862, 8870, 8880, 8881, 8890–8898, 8921, 8982, 8990, 9040–9044, 9120–9125, 9130–9133, 9135, 9136, 9141, 9142, 9161, 9170–9175, 9231, 9251, 9252, 9373, 9581	
	8830	C00.0–C39.9, C44.0–C76.8, C80.9
	8963	C00.0–C63.9, C65.9–C69.9, C73.9–C76.8, C80.9
	9180, 9210, 9220, 9240	C49.0–C49.9
	9260	C00.0–C39.9, C47.0–C75.9
	9364	C00.0–C39.9, C47.0–C63.9, C65.9–C69.9, C73.9–C76.8, C80.9
	9365	C00.0–C39.9, C47.0–C63.9, C65.9–C76.8, C80.9
e. Unspecified soft tissue sarcomas	8800–8805	C00.0–C39.9, C44.0–C76.8,
X. Germ cell tumors, trophoblastic tumors, and neoplasms of gonads		
a. Intracranial and intraspinal germ cell tumors	9060–9065, 9070–9072, 9080–9085, 9100, 9101[a]	C70.0–C72.9, C75.1–C75.3
b. Malignant extracranial and extragonadal germ cell tumors	9060–9065, 9070–9072, 9080–9085, 9100–9105	C00.0–C55.9, C57.0–C61.9, C63.0–C69.9, C73.9–C75.0, C75.4–C76.8, C80.9
c. Malignant gonadal germ cell tumors	9060–9065, 9070–9073, 9080–9085, 9090, 9091, 9100, 9101	C56.9, C62.0–C62.9
d. Gonadal carcinomas	8010–8041, 8050–8075, 8082, 8120–8122, 8130–8141, 8143, 8190–8201, 8210, 8211, 8221–8241, 8244–8246, 8260–8263, 8290, 8310, 8313, 8320, 8323, 8380–8384, 8430, 8440, 8480–8490, 8504, 8510, 8550, 8560–8573, 9000, 9014, 9015	C56.9, C62.0–C62.9
	8441–8444, 8450, 8451, 8460–8473	
e. Other and unspecified malignant gonadal tumors	8590–8671	
	8000–8005	C56.9, C62.0–C62.9
XI. Other malignant epithelial neoplasms and malignant melanomas		
a. Adrenocortical carcinomas	8370–8375	
b. Thyroid carcinomas	8010–8041, 8050–8075, 8082, 8120–8122, 8130–8141, 8190, 8200, 8201, 8211, 8230, 8231, 8244–8246, 8260–8263, 8290, 8310, 8320, 8323, 8430, 8440, 8480, 8481, 8510, 8560–8573	C73.9
	8330–8337, 8340–8347, 8350	

(continued)

TABLE 1
(continued)

Diagnostic group	ICD-O-3 code(s)[10] Morphology	Topography
c. Nasopharyngeal carcinomas	8010–8041, 8050–8075, 8082, 8083, 8120–8122, 8130–8141, 8190, 8200, 8201, 8211, 8230, 8231, 8244–8246, 8260–8263, 8290, 8310, 8320, 8323, 8430, 8440, 8480, 8481, 8500–8576	C11.0–C11.9
d. Malignant melanomas	8720–8780, 8790	
e. Skin carcinomas	8010–8041, 8050–8075, 8078, 8082, 8090–8110, 8140, 8143, 8147, 8190, 8200, 8240, 8246, 8247, 8260, 8310, 8320, 8323, 8390–8420, 8430, 8480, 8542, 8560, 8570–8573, 8940, 8941	C44.0–C44.9
f. Other and unspecified carcinomas	8010–8084, 8120–8157, 8190–8264, 8290, 8310, 8313–8315, 8320–8325, 8360, 8380–8384, 8430–8440, 8452–8454, 8480–8586, 8588–8589, 8940, 8941, 8983, 9000, 9010–9016, 9020, 9030	C00.0–C10.9, C12.9–C21.8, C23.9–C39.9, C48.0–C48.8, C50.0–C55.9, C57.0–C61.9, C63.0–C63.9, C65.9–C72.9, C75.0–C76.8, C80.9
XII. Other and unspecified malignant neoplasms		
a. Other specified malignant tumors	8930–8936, 8950, 8951, 8971–8981, 9050–9055, 9110	
	9363	C00.0–C39.9, C47.0–C75.9
b. Other unspecified malignant tumors	8000–8005	C00.0–C21.8, C23.9–C39.9, C42.0–C55.9, C57.0–C61.9, C63.0–C63.9, C65.9–C69.9, C73.9–C75.0, C75.4–C80.9

ICD-O-3: International Classification of Diseases for Oncology, third edition; CNS: central nervous system.

[a] Tumors with nonmalignant behavior are included for all morphology codes on the line.

8.2 British Childhood Cancer Survivor Study Questionnaire

FEMALE VERSION **STRICTLY CONFIDENTIAL**

DEPARTMENT OF PUBLIC HEALTH AND EPIDEMIOLOGY

UNIVERSITY OF BIRMINGHAM

STUDY OF PEOPLE TREATED FOR CANCER, LEUKAEMIA, TUMOUR OR SIMILAR ILLNESS IN CHILDHOOD

WE WOULD PREFER YOU TO FILL IN THE FORM, BUT IF THIS WOULD BE DIFFICULT BECAUSE OF SOME DISABILITY, IMPAIRMENT OR HANDICAP THEN WE ARE HAPPY FOR A CLOSE RELATIVE OR FRIEND TO FILL IN THE FORM WITH YOU.

PLEASE ANSWER THE QUESTIONS AS FULLY AS YOU CAN, BUT IF YOU CANNOT ANSWER A QUESTION PLEASE JUST GO ON TO THE NEXT QUESTION. IF THERE IS NOT ENOUGH SPACE TO FULLY ANSWER A QUESTION, THEN PLEASE CONTINUE ON A SEPARATE SHEET AND ATTACH TO THIS FORM.

PLEASE ANSWER EACH QUESTION BY TICKING A BOX AND BY GIVING FURTHER DETAILS WHEN ASKED. WHEN YOU HAVE FILLED IN THE FORM PLEASE RETURN IT TO US IN THE ENVELOPE ENCLOSED – NO STAMP IS NEEDED.

PLEASE WRITE CLEARLY.

If you have any questions about the form or the study then please telephone the Birmingham Study Centre, free of charge, on

☎ ☎

A member of the study team will answer your call between 9am and 6.30pm (Monday to Friday). An answerphone will record your message at other times.

If you would like to speak with someone either inside or outside of our office hours, but you are unable to call between 9am and 6.30pm, then please leave your telephone number together with some preferred days and times on the answerphone and a member of the study team will call you back.

A