ADVERSE HEALTH OUTCOMES AMONG LONG-TERM SURVIVORS OF CHILDHOOD, TEENAGE AND YOUNG ADULT CANCER

by

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ABSTRACT

Survivors of childhood, teenage and young adult cancer are at increased risk of developing adverse health outcomes. This thesis aims to address the gaps in knowledge regarding the most severe adverse health outcomes.

The Teenage and Young Adult Cancer Survivor Study (TYACSS) provides 200,945 survivors of cancer diagnosed aged 15-39 years. The PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies (PanCareSurFup) provides 69,460 survivors of cancer diagnosed aged <20 years.

Within the TYACSS cohort 1) cancer survivors had increased risk of developing subsequent primary neoplasms, particularly in previously irradiated sites; 2) cancer survivors who likely received cranial irradiation had increased risk of a cerebrovascular event; and 3) central nervous system tumour survivors experienced premature mortality due to neoplastic and non-neoplastic causes. Within the PanCareSurFup cohort 1) the excess number of subsequent soft-tissue sarcoma was low, except leiomyosarcoma after retinoblastoma; and 2) the excess number of subsequent breast cancers remained elevated beyond 40 years of age among survivors of Hodgkin lymphoma, Wilms tumour and sarcoma.

This thesis focuses on the most severe adverse health outcomes among childhood, teenage and young adult cancer survivors and provides evidence for developing clinical follow-up guidelines aimed at reducing such adverse health outcomes.

To my family

"You've been to three different universities now, I think it's time you got yourself a job!" – Amber Bright, 7 years old.

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- Poster presentation: "Cause-specific mortality in 24,111 5-year survivors of Central Nervous System tumours diagnosed under age 40."
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National Cancer Intelligence Network Cancer Outcomes Conference. Birmingham, UK, 2014.

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13th PanCare Meeting. Wroclaw, Poland, May 2014.

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LIST OF ABBREVIATIONS

A L leukaemia (ALL) – Acute lymphoblastic leukaemia

A M leukaemia (AML) – Acute myeloid leukaemia

AER – Absolute excess risk

AHA – American Heart Association

ASA – American Stroke Association

AYA – Adolescent and young adult

BCCSS – British Childhood Cancer Survivor Study

BRFSS – Behavioural Risk Factor Surveillance System

BRCA1 – Breast cancer gene 1

BRCA2 – Breast cancer gene 2

C M leukaemia – chronic myeloid leukaemia

CAG – Confidentiality Advisory Group

CCSS – Childhood Cancer Survivor Study

CI – Confidence interval

COG – Childhood Oncology Group

CNS – central nervous system

CV – cerebrovascular event

DCOG – Dutch Childhood Oncology Group

EHR – Excess hospitalisation ratio

E – Expected number

FPN – First primary neoplasm

GPRD – General Practice Register Database

Gray - Gy

GU – Genitourinary

HB – Hospital-based

HES – Hospital Episode Statistics

HL – Hodgkin lymphoma

IACR – International Association of Cancer Registries

IARC – International Agency for Research on Cancer

ICCC – International Classification for Childhood Cancer

ICD – International Classification of Diseases

ICD-O – International Classification of Diseases for Oncology

IGHG – International Guideline Harmonisation Group

MINAP – Myocardial Ischaemia National Audit Project

MPNST – Malignant peripheral nerve sheath tumour

NCI – National Cancer Institute

NEC – Not elsewhere classified

NHL – Non-Hodgkin lymphoma

NHS – National Health Service

NMSC – Non-melanoma skin cancer

NOS – Not otherwise specified

NRES – National Research Ethics Service

O – Observed number

ONS – Office for National Statistics

PanCareSurFup – The PanCare Childhood and Adolescent Survivor Care and Follow-up Studies

PB – Population-based

PEDW – Patient Episode Database for Wales

PNET – Primitive neuroectodermal tumour

PY – Person-years

RB – Retinoblastoma

RB1 – Retinoblastoma protein

REF - Reference

RER – Relative excess risk

RR – Relative risk

RS – Relative survival

RT – Radiotherapy

RTDS – National Radiotherapy Dataset

SACT – Systematic Anti-Cancer Therapy

SEER – Surveillance Epidemiology and End Results

SIGN – Scottish Intercollegiate Guideline Network

SIR – Standardised incidence ratio

SMR – Standardised mortality ratio

SPN – Subsequent primary neoplasm

STS – Soft-tissue sarcoma

SHR – Standardised hospitalisation ratio

TP53 – Tumour protein p53

TYA – Teenagers and young adults

TYACSS – Teenage and Young Adult Cancer Survivor Study

UK – United Kingdom

UKCCLG – United Kingdom Childhood Cancer and Leukaemia Group

WHO – World Health Organisation

Chapter 1

Introduction

The purpose of this chapter is to introduce and provide a background of the topics that will be investigated and discussed throughout this thesis. This chapter will provide a background of i) teenage and young adult cancers, ii) childhood cancers, and iii) long-term clinical follow-up guidelines for cancer survivors. In addition, a description of the cohorts used in each chapter will be provided and the rationale and structure of the thesis will be described.

1.1 TEENAGE AND YOUNG ADULT CANCER

Teenage and young adult (TYA) cancer patients have been acknowledged as an understudied population[1-3] and have been described as a "lost tribe" between paediatric and adult oncology[4]. Inconsistent definitions with regards to the age range of TYA cancer patients have hampered the development of guidelines for the care and follow-up of TYA cancer patients. Thus far, the definitions of TYA have included one of the following age ranges: 13-24 years[5], 15-24 years[6], 15-29 years[7, 8] or 15-39 years[1, 9-11]. The National Cancer Institute (NCI) proposed the latest definition of TYA cancer to include patients diagnosed with a malignant neoplasm (including all intracranial neoplasms regardless of behaviour) when aged 15-39 years[1]. The lower limit of age 15 years was chosen as the number of patients receiving specialist paediatric care declines around this age. The upper limit of age 39 years was chosen as these patients will have reached pubertal maturation, but will not have reached ages at which the risk of developing mature onset morbidities start to increase in the general population. In addition these patients often identify more with their younger counterparts as opposed to the older population of cancer patients[1].

As the spectrum of cancers diagnosed in the TYA population is different to that observed among children and mature adults Birch *et al.* proposed and developed a new classification

for grouping TYA cancers[6] which is based on the International Classification for Disease Oncology (ICD-O)[12] and which was later refined by Barr *et al*[13]. The proposed TYA classification grouped cancers into ten main categories representing the most commonly diagnosed neoplasms between 15 and 39 years of age comprising: 1) leukaemia, 2) lymphoma, 3) central nervous system (CNS) tumours, 4) bone tumours, 5) soft-tissue sarcomas, 6) germ cell neoplasms, 7) malignant melanoma, 8) carcinomas, 9) miscellaneous specified neoplasms and 10) unspecified malignant neoplasms. Seven of these categories— excluding germ cell tumours, carcinomas and unspecified malignant neoplasms— were further divided into histological subtypes. Germ cell tumours and carcinomas were further categorised by tumour anatomical location[6, 13]. Carcinomas were grouped as one category within the TYA classification as it was originally developed for cancers diagnosed in individuals aged 15-24 years, for whom carcinomas are less common than other cancers (e.g. lymphomas, leukaemia, and germ cell tumours). However carcinomas are much more common in the individuals diagnosed within the older TYA age range (25-39 years), therefore the subcategories within carcinomas provides information on the distribution of carcinomas observed in this age range.

Currently available United Kingdom (UK) incidence and survival figures are restricted to TYA cancer diagnosed age 15-24 years[6, 14], thus to provide incidence and survival relating to the most recent definition of TYA cancer (15-39 years) paragraphs 1.1.1 and 1.1.2 below refer to incidence and survival of TYA cancer in Europe, for which the most inclusive figures are available.

1.1.1 Incidence

Approximately 66,000 patients are diagnosed with TYA cancer (age 15-39) each year in Europe—constituting 2% of all cancer registrations[10]. The most frequently diagnosed TYA cancers are: carcinomas (47%), malignant melanoma (14%), germ cell tumours (13%) and lymphomas (12%)[10] (Figure 1.1). However the distribution of tumour types varies as a function of age within the TYA age span (Figure 1.2). The most common tumours in 15-19 year olds are: Hodgkin lymphoma (21%), germ cell tumours (14%) and leukaemia (12%)[10]. The most common tumours in 25-29 year olds are: germ cell tumours (20%), melanoma (16%), and genital tract neoplasms in women (10%)[10]. The most common tumours in 35-39 year olds are: carcinomas, particularly breast carcinomas (27%), and genital tract carcinomas in women (13%)[10]. The incidence of TYA cancer increases with age (Figure 1.3) with approximately 45% and 35% of TYA cancers diagnosed aged 35-39 years for women and men, respectively[10].

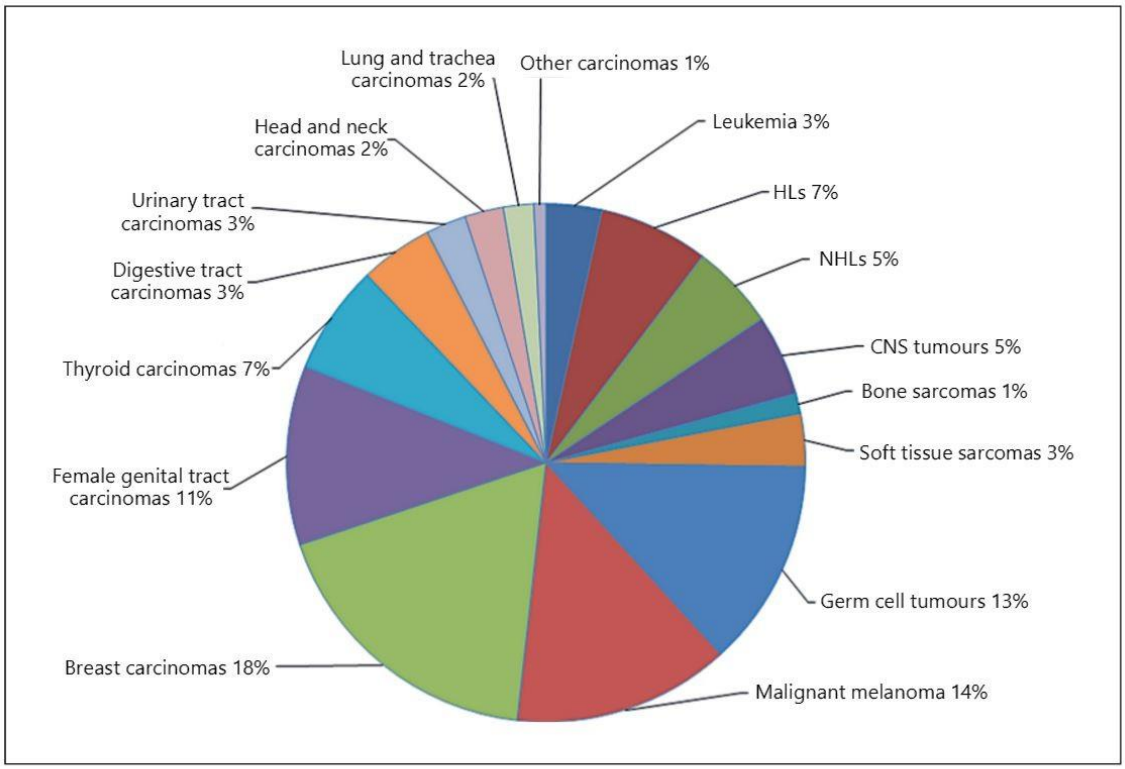


Figure 1.1: Distribution of TYA cancers diagnosed in individuals aged 15-39 years in Europe[10]

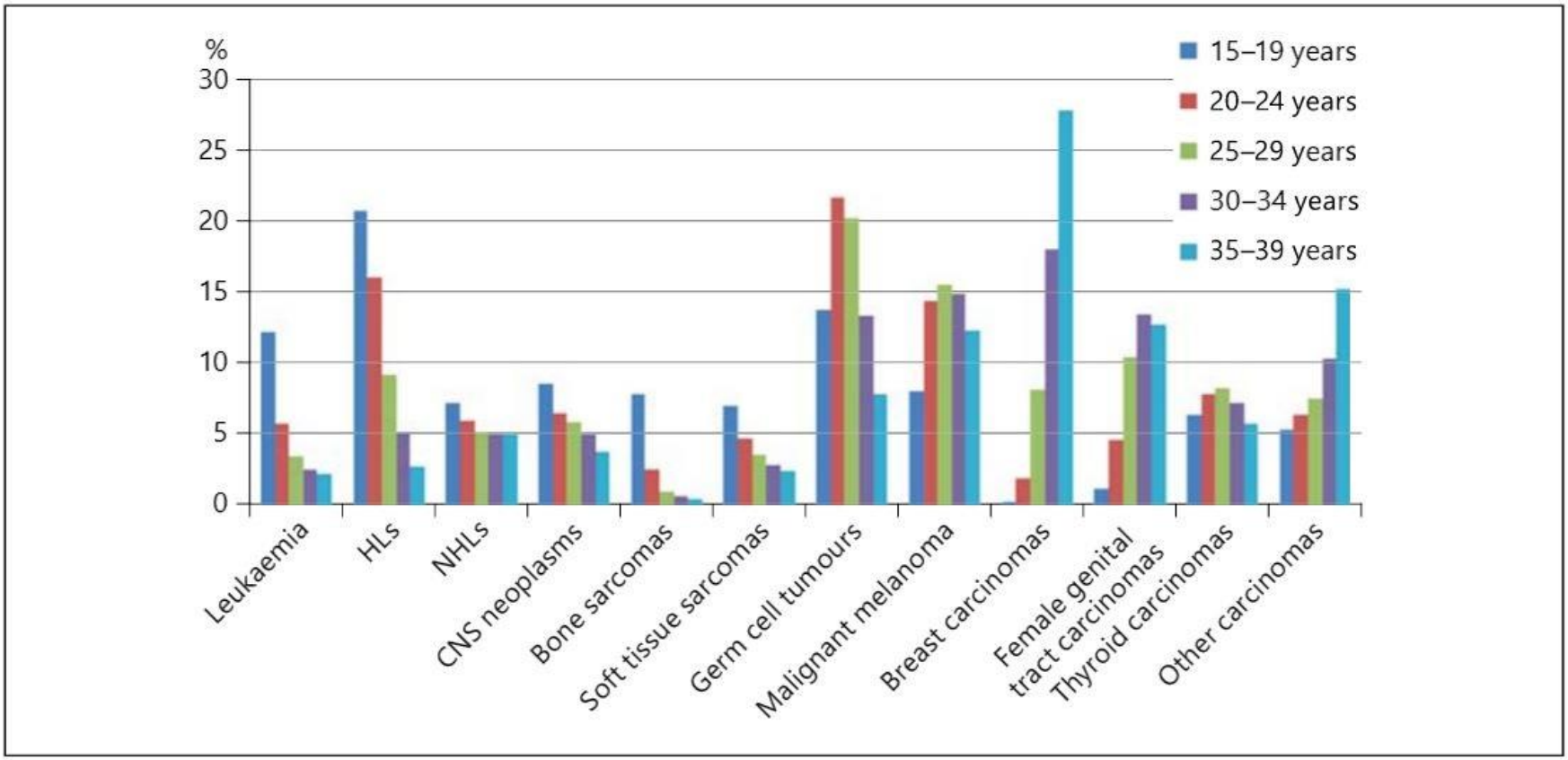


Figure 1.2: Proportion of TYA cancer types by age group in Europe [10]

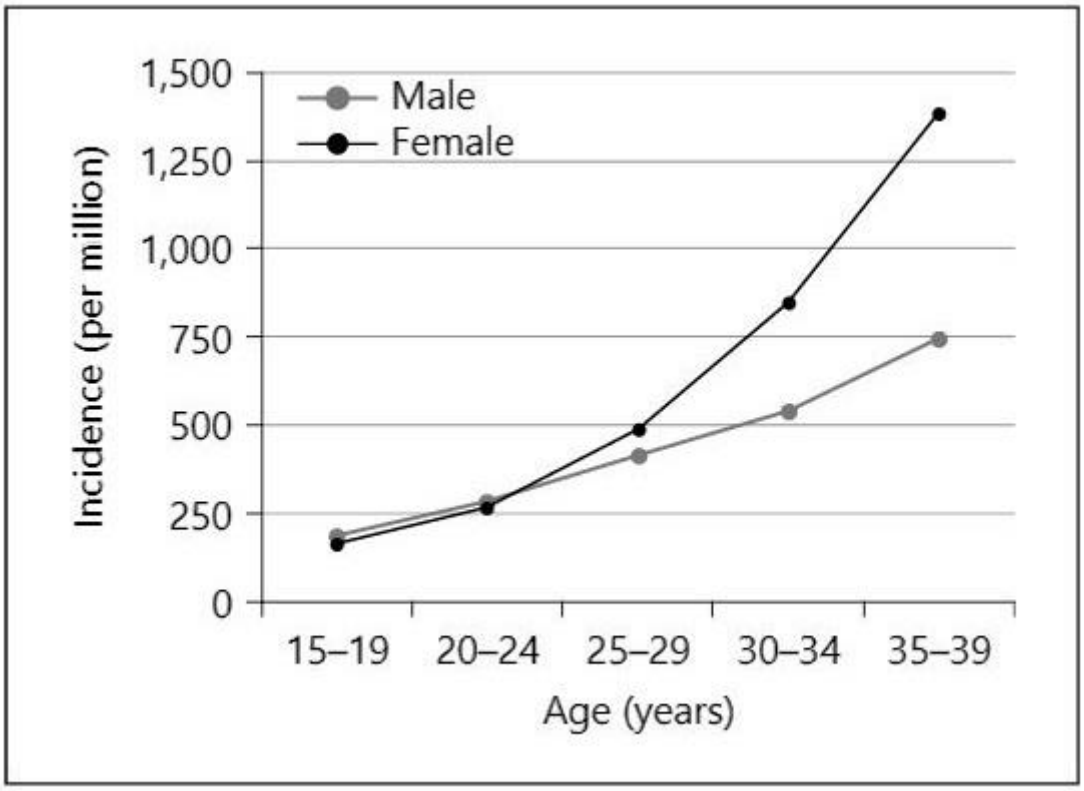


Figure 1.3: Incidence of TYA cancer by age group and gender in Europe[10].

1.1.2 Survival

Survival from TYA cancer has improved with the current European 5-year relative survival at 80%[11]. Five-year relative survival is consistently, albeit only slightly, higher among women than men (Table 1.1); this probably caused by a higher rate of cancer types with poorer outcomes in men than in women[10]. Survival varies considerably depending on the type of TYA cancer—thyroid carcinomas, gonadal germ cell tumours and Hodgkin lymphoma have an extremely high five-year relative survival (>90%); in contrast, liver carcinomas, lung carcinomas and rhabdomyosarcoma have an extremely poor relative survival (<40%)[10, 11]. Five-year relative survival is poorer in TYA patients than children for acute lymphoid

leukaemia, acute myeloid leukaemia, Hodgkin lymphoma, non-Hodgkin lymphoma, rhabdomyosarcoma, Ewing's sarcoma of the bone and osteosarcoma. However in general, TYA patients have a higher five-year relative survival than adult patients except for breast, prostate and colorectal carcinomas[11].

Table 1.1: five-year relative survival (RS) of TYA cancer in Europe stratified by age group and gender[10].

Age at diagnosis, years	5-Year RS, %		
	male and female	male	female
15–19	79.5	77.4	82.0
20–24	83.3	81.5	85.4
25–29	83.6	83.2	84.1
30–34	81.7	80.0	82.8
35–39	78.7	73.9	81.3

1.1.3 Adverse health outcomes

The high survival among TYA cancer survivors has led to a large population who are at increased risk of adverse health outcomes later in life. Many adverse health outcomes develop as a complication of treatment for cancer and can occur many decades after treatment has finished[3, 15]. TYA cancer survivors still have many decades of life to live; therefore it is particularly important that the risk of developing adverse health outcomes is investigated with the ultimate aim of reducing the number of survivors affected in the future.

A cross-sectional study of TYA cancer survivors diagnosed age 15-39 years in the United States reported that 30% of TYA cancer survivors in their 40s, 50s and 60s reported poor health compared to less than 20% of the general population of the same age[16]. In a similar study, TYA cancer survivors reported a higher prevalence of chronic conditions, disability, poor mental health and poor physical health than individuals without a history of cancer[17]. Several studies have reported that TYA cancer survivors experience a greater number of hospitalisations than the general population[18-22], however only one study has focused on the whole spectrum of TYA cancer survivors aged 15-39 years[18]. Rugbjerg and Olsen[18] reported that the standardised hospitalisation ratio (SHR) among Danish TYA cancer survivors was highest for diseases of the blood (SHR=2.0), infectious and parasitic diseases (SHR=1.7), and subsequent primary neoplasms (SPNs) (SHR=1.6); whilst the absolute excess risk (AER) was highest for SPNs (AER=50 per 10,000 person-years), diseases of the digestive organs (AER=42 per 10,000 person-years), and diseases of the circulatory system (39 per 10,000 person-years). Within the Danish cohort, survivors of leukaemia, brain tumours and Hodgkin lymphoma had the highest risk of hospitalisation than in the general population with 2.2-fold, 1.9-fold and 1.9-fold increased risk, respectively.

Previous literature suggests that TYA cancer survivors are at an increased risk of premature mortality[22-28], subsequent primary neoplasms (SPNs)[7, 18, 24, 29-38], circulatory disease[18, 20, 21, 39-42], pulmonary disease[18, 20, 21, 26, 43, 44], adverse obstetric and perinatal outcomes[45-48], gastrointestinal disease[18, 20, 21], and endocrine disease[18, 20]. However, the majority of these previous studies of adverse health outcomes have focused on either survivors of childhood and adolescent cancer only or on adult cancers irrespective of age at diagnosis; few have

focused on survivors of cancer diagnosed aged 15-39 years. The type, distribution and biology of TYA cancer is distinct from childhood and adults cancers[49], therefore more evidence focusing on survivors of cancer when aged 15-39 years is required.

The following three sections describe the available literature regarding the most severe and potentially life-threatening adverse health outcomes experienced by cancer survivors: premature mortality, SPNs and circulatory disease. These adverse health outcomes are the focus of this thesis.

1.1.3.1 Premature mortality

A few studies have reported an increased risk of premature mortality among subsets of TYA cancer survivors[22-28]; however no study has focused on the whole spectrum of TYA cancer survivors diagnosed aged 15-39 years. A study using data from the Finnish Cancer Registry observed a 4.2-fold risk of all-cause mortality among cancer survivors diagnosed aged 20-34 years[23] when compared to the general population. Similar estimates were observed among cancer survivors aged 20-24 years in British Columbia (5.9-fold)[24], aged 15-24 years in Scotland (4.7-fold)[25] and aged 15-20 years in the North American Childhood Cancer Survivor Study (CCSS) (7.9-fold)[27]. Within the Finnish cohort the standardised mortality ratio (SMR) for all-cause mortality was highest among survivors of CNS tumours (12.3-fold) and acute lymphoblastic leukaemia (14.2-fold)[23]. The SMR for all-cause mortality was also highest among CNS tumour survivors (23.6-fold) in Scotland[25]. The most frequent causes of death in the Finnish TYA cohort were death due to neoplastic causes (recurrence/progression of the TYA tumour and SPNs), and cardiovascular diseases[23]. Variation in the distribution of causes of excess deaths beyond that expected from the general population with increasing years from

diagnosis from TYA cancer has not been investigated. Among childhood cancer survivors the number of excess deaths is greatest due to progression or recurrence of the childhood cancer in the initial years after diagnosis, however as time progresses SPNs, cardiovascular disease and other non-neoplastic causes of death account for the vast majority of the number of excess deaths[50]. Knowledge regarding the variation in the distribution of causes of death as years from diagnosis increases is vital to guide preventative strategies concerning premature mortality; because it would provide information on what diseases/outcomes preventative measures need to be focussed on.

1.1.3.2 Subsequent primary neoplasms

A SPN is defined as the development of a further neoplasm that is not a recurrence or progression of the first primary neoplasm and is histologically distinct from the first primary neoplasm. A study using data from the Surveillance Epidemiology and End Results (SEER) registries is the only study that has investigated the risk of developing a SPN in the whole spectrum of TYA cancers diagnosed age 15-39 years[29]. The standardised incidence ratio (SIR) of developing a SPN was 1.6-fold compared to the general population and the cumulative risk at 30 years from diagnosis of a TYA cancer was 13.9%[29]. Survivors of Hodgkin lymphoma, breast cancer, acute myeloid leukaemia, non-Hodgkin lymphoma, testicular cancer and sarcomas had an increased risk of developing a SPN than that expected from the general population. The risk of developing a SPN among individuals aged 20-24 in British Columbia was 3-fold that expected from the general population; and was highest for SPNs in the respiratory system, digestive system, breast and endocrine glands[24]. The risk of developing a SPN among survivors of cancer diagnosed aged 15-29 years in the Netherlands was 3.1-fold and 2.0-fold that expected for men and women, respectively[7]. Several studies have

investigated the risk of specific SPNs among survivors of cancers that are relatively common among TYAs, but also included those diagnosed at any age[30-38]. Among these studies there was useful information relating to TYA for survivors of Hodgkin lymphoma and testicular cancer and this will be discussed in more detail in the following two sections.

1.1.3.2.1 SPNs after Hodgkin lymphoma

There is a considerable amount of literature describing the increased risk of developing a SPN among Hodgkin lymphoma survivors[31, 36-38, 51-54]. A large Dutch study of Hodgkin lymphoma survivors diagnosed aged 15-49 years reported increased risks of cancer of the oral cavity, gastrointestinal tract, lower respiratory system, skin, soft-tissue, breast (women), genital tract (women), urinary tract, thyroid gland and haematopoietic system[36]. From several case-control studies there are reports of a linear dose-response relationship between cumulative dose of radiation from radiotherapy to the chest and the risk of breast cancer in women[55-57]. The vast amount of evidence regarding the association of chest radiotherapy and the development of breast cancer has led to the development of clinical follow-up guidelines which recommend women treated with high dose chest radiotherapy (≥20 Gy) before age 30 to undergo breast cancer surveillance from age 25 or 8 years after treatment, whichever occurs last[58]. From several case-control studies there are reports of a linear dose-response relationship between cumulative dose of radiation from radiotherapy and the risk of lung cancer among Hodgkin lymphoma survivors[51-53]. There are contrasting reports as to whether lung cancer risk is increased with increasing number of cycles and cumulative dose of chemotherapy; further investigations are needed[51-53].

1.1.3.2.2 SPNs after testicular cancer

Testicular cancer is the most frequent TYA cancer diagnosed among men and has an extremely high relative survival with five-year survival at 97.8% for patients diagnosed age 15-39 years[59]. However, it has been well documented that testicular cancer survivors are at increased risk of developing an SPN[33, 35, 41, 60]. Testicular cancer survivors treated with adjuvant infradiaphragmatic irradiation for potential lower-abdomen metastasis have a 1.5-2.7-fold increased risk of developing a SPN, particularly SPNs occurring within the radiotherapy field such as bladder, stomach, pancreas or kidney[33, 41, 60]. Infradiaphragmatic radiotherapy increases the risk of SPNs in a dose-dependent manner[41]. Testicular cancer survivors are also at an increased risk of subsequent primary leukaemia[61, 62]; this increased risk has been associated with the use of platinum-based chemotherapeutic agents such as Cisplatin[62].

1.1.3.3 Circulatory disease

Rugbjerg *et al* observed a 30% increased SHR for cardiovascular disease among a cohort of Danish cancer survivors diagnosed aged 15-39 years[39] and an excess persisted up to 50 years from TYA cancer diagnosis, leading to a large excess number of cardiovascular diseases being observed beyond that expected from the general population[39]. Cardiovascular diseases included hypertension, ischaemic heart disease, pulmonary heart disease, valvular heart disease, cardiomyopathy, arrhythmia, cerebrovascular disease, arterial disease, and venous & lymphatic disease. A smaller study of cancer survivors diagnosed age 15-29 years in Yorkshire did not report an increased risk of hospitalisation for cardiovascular disease overall, however did report increased number of hospitalisations for pericardial disease, cardiomyopathy and heart failure, pulmonary heart disease, conduction disorders, and

hypertension[8]. Among a cohort of Hodgkin lymphoma survivors diagnosed before age 41, Aleman *et al*[40] reported almost 4-fold the expected number of myocardial infarctions and 5-fold the expected number of congestive heart failures. Treatment with mediastinal radiotherapy and anthracyclines was associated with increased risk of cardiac disease among this population of Hodgkin lymphoma survivors. Furthermore, cohorts of adult and childhood cancer survivors have also reported increased risks of cardiac disease after treatment with mediastinal radiotherapy and anthracyclines[40, 63-67]. Among another cohort of Hodgkin lymphoma survivors, who were diagnosed before age 51, De Bruin *et al*[42] reported 2-fold and 3-fold the expected number of strokes and transient ischaemic attacks, respectively. Radiotherapy to the neck and mediastinum was associated with an increased risk of stroke among this population of Hodgkin lymphoma survivors. Furthermore, radiation to the head and neck has been associated with increased risk of stroke among cohorts of adult head and neck tumour survivors[68-71]. Among survivors of childhood cancer, cranial radiotherapy has also been associated with increased risk of strokes[72-74].

1.2 CHILDHOOD CANCER

Childhood cancer is predominantly defined as a diagnosis of cancer among patients aged 0-14 years inclusive[75]. In addition to patients aged 0-14 years, many cohorts of childhood cancer survivors are also supplemented by patients diagnosed as adolescents up to age 20 years inclusive[76-78]. Childhood cancers are commonly grouped according to the hierarchical International Classification for Childhood Cancers (ICCC)[79]. Several histological types of childhood cancer can appear in numerous anatomical sites; therefore the ICCC classifies childhood cancer by tumour histology (International Classification for Disease Oncology

[ICDO]) rather than the anatomical site (International Classification of Diseases [ICD]) that is often used to group adult cancers. The 12 main diagnostic groups within the ICCC are: 1) leukaemia, 2) lymphomas and reticuloendothelial neoplasms, 3) CNS tumours, 4) neuroblastoma, 5) retinoblastoma, 6) renal tumours (including Wilms tumour), 7) hepatic tumours, 8) bone tumours, 9) soft-tissue sarcomas, 10) germ cell tumours, 11) other malignant epithelial neoplasms and malignant melanoma, 12) other and unspecified neoplasms. These main diagnostic groups are further divided according to important entities or by tumours that have similar characteristics[79].

Many childhood cancer survivor cohorts include adolescents (15-19 years or 15-20 years) in addition to children (0-14 years), however the incidence and survival for these individuals was included in the age range of TYA cancer and has been described in sections 1.1.1 and 1.1.2. Therefore, sections 1.2.1 and 1.2.2 describe the incidence and survival of childhood cancer diagnosed before age 15 only.

1.2.1 Incidence

Childhood cancer is rare and constitutes less than 1% of all cancer registrations each year in the UK[75]. The most common cancers diagnosed in children are: leukaemia (31%), CNS tumours (26%) and lymphomas (10%) (see figure 1.4)[80]. Childhood cancer is commonly diagnosed under age five with 49% of all childhood cancers diagnosed in this age group. The distribution of tumour types varies as a function of age—acute lymphoblastic leukaemia (ALL), neuroblastoma, Wilms tumour, hepatic tumours and retinoblastoma peak in children under age five, whereas bone tumours and Hodgkin lymphomas peak in adolescents[75, 80].

An increase in incidence of childhood cancer has been observed for all regions of Europe[81]. There is slight variation in the world age standardised incidence rate of childhood cancer within Europe. In the period 1988-1997, the incidence of childhood cancer was highest in northern Europe (incidence rate = 160 per million) and lowest in the British Isles (incidence rate = 131 per million).

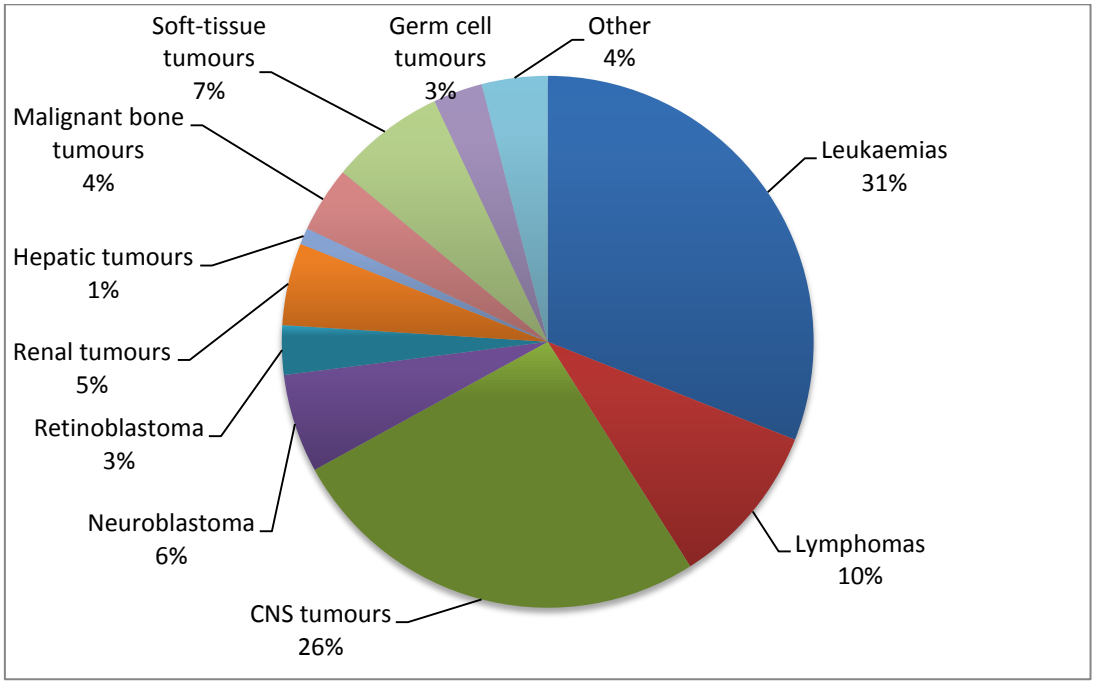


Figure 1.4: Main types of childhood cancer in the United Kingdom from 2001 to 2010 [80]

1.2.2 Survival

Survival from childhood cancer has improved dramatically since the late 1960s due to major advances in anti-cancer treatments. In Great Britain, five-year relative survival for all childhood cancers combined increased from 28% for children diagnosed in 1966-1970 to 82% for children diagnosed in 2006-2010[75, 82]. Survival has improved over recent decades for all of the 12 childhood cancer diagnostic groups in ICCC and five-year survival increased

substantially between 1966-1970 and 1971-1975 for leukaemia, lymphoma and Wilms tumour (renal tumours)[75]. The introduction of combination chemotherapy in the late 1960s and early 1970s in addition to inductions into clinical trials is largely responsible for this increase in survival[83]. Similar to estimates from Great Britain, survival from childhood cancer in Europe has improved over the past few decades. However, there are still disparities in survival between European countries especially for Eastern Europe who present the lowest five-year survival (60-77%)[84].

1.2.3 Adverse health outcomes

The increase in survival of childhood cancer has resulted in a large population of survivors—estimated to be between 300,000 and 500,000 in Europe—who are at increased risk of developing long-term adverse health outcomes as a result of the cancer or treatment[85]. As each childhood cancer survivor still has the whole of their adult life ahead of them; the development of one or multiple adverse health outcomes may have a severe impact on their quality of life; or worse, may even result in premature mortality. The development of adverse health outcomes depends on numerous factors such as the type of childhood cancer, age at diagnosis of the childhood cancer, gender, and the type and cumulative dose of treatment exposures received[86, 87]. Among the CCSS, 62% of childhood cancer survivors reported at least once chronic health condition and 28% reported at least one severe or life-threatening condition[88]. A higher proportion of Dutch childhood cancer survivors reported having at least one chronic health condition (40%) and at least one severe or life-threatening condition (40%)[89]. In addition, 55% of Dutch patients who received radiotherapy reported a high or severe burden of adverse health outcomes[89]. Survivors of bone tumours, CNS tumours and Hodgkin lymphoma reported the highest number of severe or life-threatening conditions[88, 89].

Childhood cancer survivors have an increased risk of numerous severe adverse health outcomes including: premature mortality, SPNs, circulatory complications, endocrine complications, neurological dysfunction, pulmonary complications, urological complications, gonadal disorders, muscoskeletal disorders and gastrointestinal disorders[86, 87, 90, 91].

The following paragraphs provide a summary of those adverse health outcomes experienced by childhood cancer survivors that account for the greatest number of excess deaths among mature survivors including premature mortality overall, SPNs and cardiovascular disease[50, 92].

1.2.3.1 Premature mortality

The most severe adverse health outcome among long-term survivors of childhood cancer is premature mortality. The risk of mortality among childhood cancer survivors is 8.3-10.7 times that expected from the general population[27, 50, 92, 93]. Among the Childhood Cancer Survivor Study (CCSS), a large cohort of childhood cancer survivors diagnosed before age 21 in America, 30% of five year survivors had died by 50 years of age when 6% would have been expected to have died[92]. The three largest studies worldwide—the CCSS, British Childhood Cancer Survivor Study (BCCSS), and a Nordic cohort—all reported a significant decline in all-cause mortality, mortality due to recurrence/progression of the childhood tumour, and non-neoplastic causes of death with more recent diagnostic period (CCSS: 1970-1999, BCCSS: 1940-2006, Nordic:1960-1999); however they report conflicting evidence as to whether this decrease is observed for death due to SPNs or not[50, 94, 95]. The progression/recurrence of childhood cancer accounts for most of the excess number of deaths observed up to age 30 years[50]. However as childhood cancer survivors age, the causes of death accounting for the

greatest number of excess deaths are SPNs and circulatory disease accounting for 31% and 37% of the total excess number of deaths beyond age 60 years[50].

1.2.3.2 Subsequent primary neoplasms

Childhood cancer survivors have a 3.3 to 11.2 fold increased risk of developing a SPN than that expected from underlying general populations with a similar demographic structure [96-104].The risk of developing a SPN depends on the primary cancer diagnosis, genetic predisposition to cancer, age at treatment, years from diagnosis and the type and dose of treatment received[90]. Furthermore, studies with long follow-up have reported that attained age is an important risk factor for the development of SPNs[98, 100]. Studies of childhood cancer survivors have reported an increased risk of solid SPNs after treatment with radiotherapy[96, 102, 104-106] and an increased risk of leukaemia after treatment with chemotherapy[96, 97, 107]. Associations between particular radiotherapy or chemotherapy treatments and the risk of specific SPNs have been established and will be discussed below.

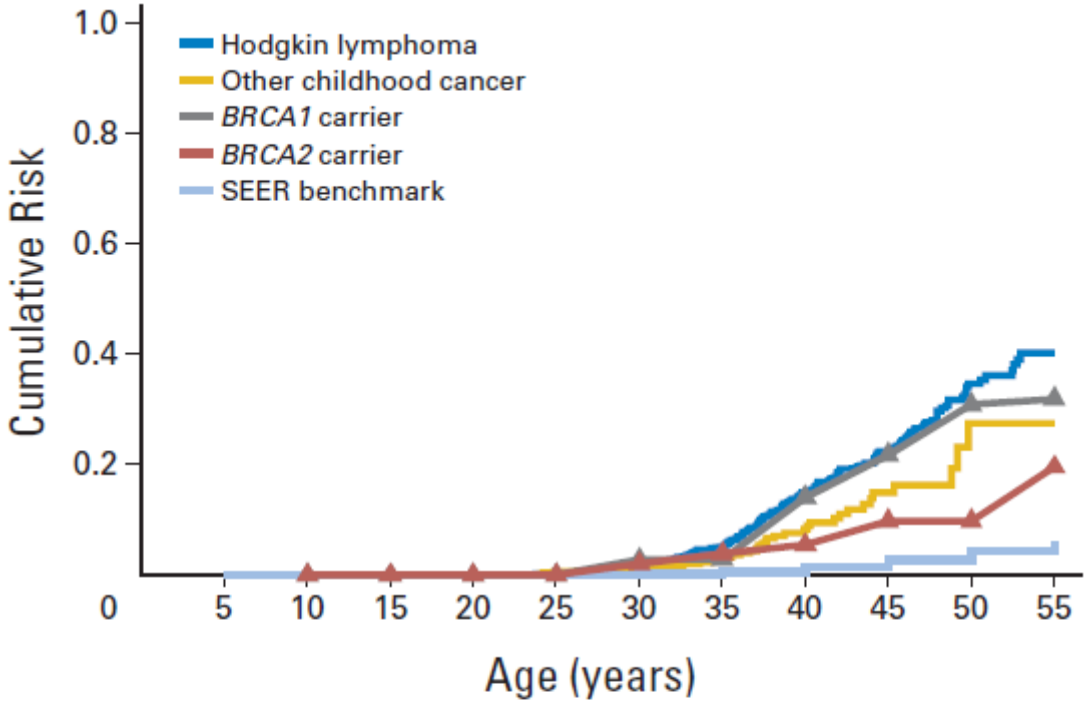
Childhood cancers treated with chemotherapy including alkylating agents and topoisomerase II inhibitors (including Etoposide) have an increased risk of developing acute myeloid leukaemia (AML) and myelodysplasia[96, 97, 107-111]. Among survivors of childhood cancer diagnosed aged under 18 years between 1973 and 2002 in the SEER registries, the risk of developing AML was 29-fold that expected among childhood cancer survivors treated with chemotherapy compared to 3-fold that expected among those not treated with chemotherapy[96]. Radiotherapy is a known risk factor for the development of subsequent primary bone and soft-tissue sarcomas[112-115]. Several studies have observed a dose-dependent relationship of radiation and the development of bone and soft-tissue sarcomas[113-115].

Sarcomas are also associated with genetic predisposition syndromes such as constitutional mutations in the RB1 gene[116, 117] and Li-Fraumeni (p53) syndrome[118]; these syndromes are associated with an increased sensitivity to radiation and the development of SPNs[117, 119, 120].

Chest radiotherapy is often used to treat childhood cancers such as Hodgkin lymphoma or cancers that have metastasised to the lungs (for example, Wilms tumour). Chest radiotherapy increases the risk of tumours developing in organs that are located within the radiation field such as the breast[38, 55, 57, 121-126]. The risk of breast cancer in female childhood Hodgkin lymphoma survivors, for which high-dose chest radiation is often used is extremely high and is comparable or higher than breast cancer risk among BRCA1 and BRCA2 carriers[38, 123, 125]. Moskowitz *et al*[123] reported that cumulative risk of breast cancer by age 50 years was 35%, 31% and 10% for childhood Hodgkin lymphoma survivors, BRCA1 carriers and BRCA2 carriers, respectively (Figure 1.5).

Children diagnosed with a CNS tumour are often treated with cranial radiotherapy and are at an increased risk of developing a subsequent primary CNS tumour[105, 127, 128]. In addition, children diagnosed with acute lymphoblastic leukaemia in the late 1960's and early 1970's were treated with cranial radiotherapy to prevent leukaemia spread to the CNS[129]. Such survivors are also at an increased risk of developing a subsequent primary CNS tumour[105, 127, 130, 131]. More recently treatment to prevent leukaemia spread to the CNS has moved towards the use of intrathecal methotrexate or cranial radiation in a small proportion of patients (<10%) who have a high risk of CNS relapse[129]. Studies from the CCSS and the BCCSS have reported a linear dose-response relationship between the cumulative amount of radiation exposure to the cranium and the risk of developing subsequent primary gliomas and

meningioma[105, 127]. Within CNS tumour survivors in the CCSS, the cumulative incidence of developing a subsequent primary CNS tumour at 25 years from diagnosis was 7.1% for patients who received cranial radiation of 50 Gray or more compared to 1.0% for patients who were not treated with any radiotherapy[128]. The Children's Oncology Group (COG) guidelines recommend children treated with cranial radiotherapy to undergo surveillance including, annual physical examinations, annual history and MRI screening if symptoms are present[132]. The UK Children's Cancer and Leukaemia Group (UKCCLG) guidelines[133] recommend CNS tumour survivors to be educated on the risk of SPNs within the radiation field and undergo regular examination of skin lesions.



	Estimated Cumulative Risk, % (95% CI)		
	By age 40	By age 45	By age 50
Childhood cancer survivors			
Entire cohort	12 (10 to 14)	18 (16 to 21)	30 (25 to 34)
Primary cancer diagnosis			
Hodgkin lymphoma	15 (12 to 18)	22 (17 to 25)	35 (29 to 40)
Other childhood cancer*	8 (5 to 12)	15 (10 to 21)	– –
Carriers of genetic mutations			
BRCA1 carriers	14 (5 to 23)	22 (11 to 33)	31 (15 to 48)
BRCA2 carriers	5 (0 to 15)	10 (1 to 23)	10 (1 to 23)

Figure 1.5: Cumulative risk of breast cancer after childhood cancer compared with carriers of BRCA1 and BRCA2 mutations.[123]

1.2.3.3 Circulatory disease

The risk of mortality in survivors of childhood cancer due to circulatory diseases is 4.0-10.8 times that expected from the general population[27, 92, 93, 134, 135]. Childhood cancer survivors are at an increased risk of developing congestive heart failure, myocardial infarction, pericardial disease and valvular abnormalities[136]. The largest population–based study to investigate

cardiovascular late effects, a Nordic cohort of childhood cancer survivors diagnosed before age 20[137], reported that childhood cancer survivors had twice the risk of being hospitalised for a cardiovascular disease than expected from the general population. Compared to the general population, childhood cancer survivors had an increased number of hospitalisations for hypertension (2-fold), ischaemic heart disease (1.7-fold), pulmonary heart disease (3.5-fold), peri-, myo- and endocardial disease (2.9-fold), valvular disease (4.6-fold), heart failure (5.2-fold), conduction disorder (1.6-fold), cerebrovascular disease (3.7-fold), arterial disease (2.7-fold), and venous- and lymphatic disease (1.5-fold)[137]. There is strong evidence that long-term cardiac toxicity is associated with previous treatment with anthracyclines and mediastinal radiotherapy[63, 136, 138, 139]. Survivors who received such treatments may benefit from receiving long-term follow up care and surveillance for circulatory disease risk factors (diabetes, hypertension, obesity).

1.3 CLINICAL LONG-TERM FOLLOW-UP GUIDELINES

Clinical guidelines for the long-term care and surveillance of childhood cancer survivors have been produced by the Children's Oncology Group (COG)[132] in the US, The Scottish Intercollegiate Guideline Network (SIGN) in Scotland[140], The UK Childhood Cancer and Leukaemia Group (UKCCLG) in the UK[133] and The Dutch Children's Oncology Group (DCOG) in the Netherlands[141]. All of the guidelines provide recommendations for the level of follow-up, screening or surveillance that childhood cancer survivors require based on their risks of adverse health outcomes given their previous therapeutic exposures and cancer type. These guidelines are regularly updated to provide the most up-to-date recommendations based on all evidence available. However, some of the recommendations are not consistent between

guidelines. The International Guideline Harmonisation Group (IGHG) was established to provide consistent and parsimonious guidelines for international use[142]. The main aim of the IGHG is to establish, through international collaboration, a common strategy and recommendations for the surveillance to prevent, diagnose early, or treat optimally the adverse health outcomes experienced by childhood, adolescent, and young adult cancer survivors. Thus far, the IGHG has published guidelines on breast cancer[58], cardiomyopathy[143] and premature ovarian insufficiency[144]. In contrast to childhood cancer survivors, long-term follow-up guidelines are currently lacking for TYA cancer survivors.

1.4 CHILDHOOD, TEENAGE AND YOUNG ADULT CANCER SURVIVOR COHORTS

For this thesis the risk of specific adverse health outcomes has been investigated among two cohorts of cancer survivors: 1) The Teenage and Young Adult Cancer Survivor Study; and 2) The PanCare Childhood and Adolescent Cancer Survivor Care and Follow-up Studies. This section will provide an overview of the cohorts included in this thesis.

1.4.1 Teenage and Young Adult Cancer Survivor Study

The Department of Health, National Institute for Health and Clinical Excellence, and the National Cancer Research Institute have all identified a need and priority for accurate information regarding the risks of adverse health outcomes after treatment for TYA cancers[145-147]. In response to the call for information, the Teenage and Young Adult Cancer Survivor Study (TYACSS) was established with the purpose of investigating: 1) the observed and expected causes of deaths beyond five-year survival, 2) the observed and expected risks

of SPNs, 3) the observed and expected risks of non-cancer serious morbidity. The ultimate aims of these investigations are to identify specific subgroups of TYA cancer survivors who are at a substantially increased risk of developing one or more adverse health outcomes. This will aid in the development of clinical follow-up guidelines, help educate and counsel survivors, help educate health professionals and provide a basis for developing future treatment protocols from a risk as well as benefit perspective.

The Office for National Statistics (ONS) and the Welsh Cancer Registry provided all cancer registrations for 15-39 year olds between 1971 and 2006 in England and Wales. The first cancer registration for a malignant neoplasm, any intracranial or any intraspinal neoplasm per individual was taken as the TYA cancer and included in the final cohort. Any individual who had a cancer registration before age 15 was excluded from the cohort by linking with the BCCSS. All diagnostic tumour types were included with the exception of non-epithelial non-melanoma skin cancer (NMSC), as they are known to be under-ascertained due to differences in policies regarding recording of NMSC between local cancer registries[148]. The TYACSS cohort consists of 200,945 five-year survivors of cancer diagnosed aged 15-39 years in England and Wales between 1971 and 2006. Characteristics of the cohort can be found in Table 1.2. The most common diagnoses are breast (18%), testis (12%), cervix (12%) and malignant melanoma (11%). 62% of the cohort are women and 62% were diagnosed from 1990 until 2006.

The TYACSS cohort has been linked to the national death register, national cancer register and the Hospital Episode Statistics (HES) database by NHS-Digital. This linkage notifies

when a cohort participant has died (vital status, date and cause of death), developed another cancer, or has had a hospital admission.

Ethical approval was provided by the National Research Ethics Service (ref: 16/LO/0895) and permission to process information without individual consent by the National Information Governance Board (NIGB) for Health and Social Care (ref: 3-03(c)2010).

1.4.2 Process to create and quality assurance of the TYACSS cohort

All cancer registrations for patients diagnosed aged 15-39 years between 1971 and 2006, and all subsequent cancer registrations for these patients, were obtained from the Office for National Statistics. All cancer registrations were checked for missing information such as dates, behaviour codes, site codes, and morphology codes. All duplicate registrations were dropped. To provide vigorous checks, all cancer registrations were converted from their original coding classification into the 3rd revision of the International Classification of Disease for Oncology using the IARC/IACR Cancer Registry Tools conversion software. This enabled the data to be checked for errors using the IARC/IACR Cancer Registry Tools IARC/IACR check program. This program checks for inconsistencies and errors in tumour site, morphology, behaviour and sex. To distinguish between, first primary neoplasm, recurrence and subsequent primary neoplasms, the cleaned data was processed using the IARC/IACR Cancer Registry Tools Multiple Primary program. This program utilises the IARC/IACR rules for defining multiple primary tumours. Those classified as first primary neoplasms formed the TYACSS cohort. Figure 1.6 shows a flow diagram of the process used to create the TYACSS cohort from cancer registration data.

Table 1.2: Cohort characteristics of the Teenage and Young Adult Cancer Survivor Study.

	5-year	%
Total	**200,945**	**100**
Sex		
Men	76,666	38.2
Women	124,279	61.9
First Primary Neoplasm		
Breast	36,236	18.0
Testicular	24,309	12.1
Cervix	23,281	11.6
Melanoma	22,446	11.2
CNS	17,280	8.6
Hodgkin Lymphoma	16,971	8.5
Non-Hodgkin Lymphoma	9,467	4.7
Thyroid	7,809	3.9
Gastrointestinal	7,224	3.6
Soft tissue sarcoma	6,130	3.1
Leukaemia	5,073	2.5
Ovary	4,885	2.4
Bladder	4,685	2.3
Other Genitourinary*	4,672	2.3
Head & neck	3,961	2.0
Bone tumour	2,241	1.1
Lung	1,219	0.6
Other	3,056	1.5
Age at Diagnosis		
15-19	12,248	6.1
20-24	21,258	10.6
25-29	35,894	17.9
30-34	54,541	27.1
35-39	77,004	38.3
Years since Diagnosis		
5-9	38,164	19.0
10-19	77,993	38.8
20-29	53,013	26.4
30-39	28,324	14.1
40+	3,451	1.7
Attained Age at Exit		
20-29	3,677	3.0
30-39	21,391	17.2
40-49	59,433	47.9
50-59	36,607	29.5
60+	3,106	2.5
Decade at Diagnosis		
1971-1979	25,158	12.5
1980-1989	51,573	25.7
1990-1999	67,167	33.4
2000-2006	57,047	28.4

**Include genitourinary tract and kidney (excluding bladder).*

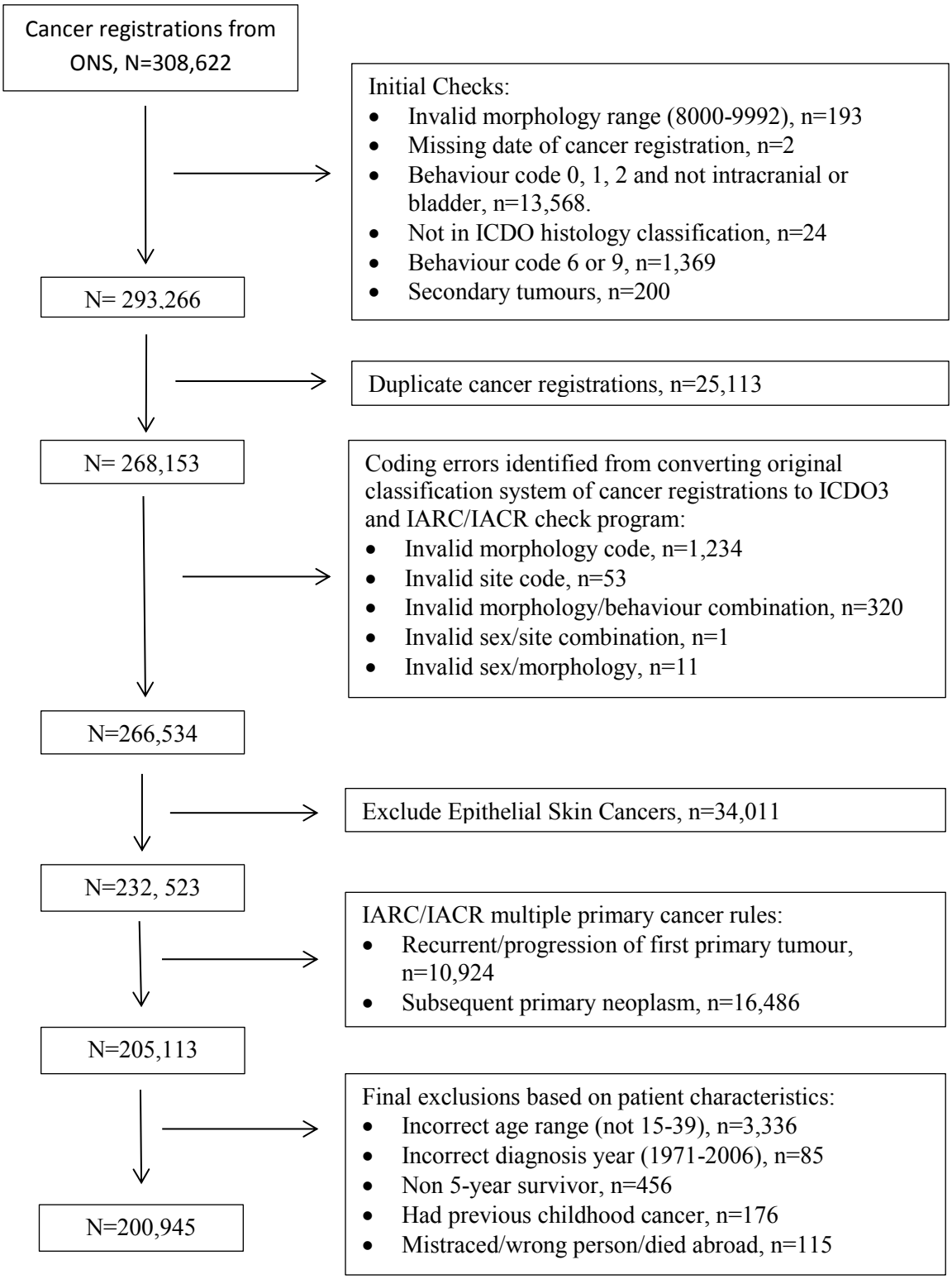


Figure 1.6: Process to create and quality assure TYACSS cohort from cancer registration data

1.4.3 PanCareSurFup

PanCare (http://www.pancare.eu/en/) is a collaborative network of healthcare professionals, epidemiologists, childhood cancer survivors and families of childhood cancer survivors across Europe[85]. This pan-European network aims to reduce the burden of adverse health outcomes from treatment among childhood and adolescent cancer survivors by providing further information and research, developing and disseminating guidelines for survivorship care and spreading awareness and knowledge regarding cancer survival[85].

The PanCare Childhood and Adolescent Cancer Survivors Care and Follow-up Studies (PanCareSurFup) (http://www.pancaresurfup.eu/) is one of the European Commission funded projects established by PanCare and aims to investigate and ultimately reduce the more serious and life-threatening adverse health outcomes observed among childhood and adolescent cancer survivors[85]. PanCareSurFup has established a retrospective European cohort of cancer survivors and this cohort will be utilised in this thesis to estimate the excess risk of specific SPNs (soft-tissue sarcoma and breast) among cancer survivors compared to the general population. Furthermore, beyond the scope of this thesis, the impact of cumulative dose of radiotherapy, cumulative dose of individual chemotherapy agents on the risk of developing subsequent genitourinary carcinomas, subsequent gastrointestinal carcinomas, subsequent bone sarcomas, subsequent soft-tissue sarcomas will be investigated using nested case-control studies.

The PanCareSurFup cohort comprises thirteen European cohorts from twelve countries to produce a pan-European cohort of 69,460 five-year survivors of childhood and adolescent cancers. The thirteen cohorts consisted of eleven population-based cohorts from Hungary,

Italy, The Netherlands, Denmark, Sweden, Norway, Finland, Iceland, Slovenia, Switzerland and the UK, and two treatment centre cohorts from France and Italy. Ethical approval for each cohort was obtained from the appropriate bodies within each of the countries. To be eligible for inclusion, participants had to have a cancer diagnosis before age 20 in one of the participating cohorts and have survived for at least five years. Characteristics of the cohort and the diagnostic periods of each country are shown in Table 1.3 and Table 1.4, respectively.

The British Childhood Cancer Survivor Study (BCCSS) cohort provided the UK contribution to PanCareSurFup. The BCCSS is a cohort of cancer survivors diagnosed before the age of 15, thus there was no overlap with the previously described TYACSS cohort of TYA cancer survivors.

1.4.4 Process to create and quality assurance of the PanCareSurFup cohort

Each country participating in PCSF sent relevant childhood cancer cohort data to the data-coordinating centre in Mainz, Germany, which was the lead organisation for data collection and harmonisation for the PanCareSurFup study. The coordinating centre performed validity checks on the data and combined the data from each individual country into one overall cohort of childhood cancer survivors. The entire cohort dataset was then transferred to Birmingham and the Centre's IT-manager, and myself carried out further checks. To provide rigorous checks, all cancer registrations were converted from their original coding classification into the 3rd revision of the International Classification of Disease for Oncology using the IARC/IACR Cancer Registry Tools conversion software. This enabled the data to be checked for errors using the IARC/IACR Cancer Registry Tools IARC/IACR check program. Any errors or inconsistencies were discussed with each individual data provider and corrected

where required. To enable comparison with other studies, childhood cancers were classified according to the 3rd revision of the International Classification of Childhood Cancers (ICCC3). Tumours that were not classifiable to ICCC3 were excluded from the cohort. The process used to finalise the PanCareSurFup cohort is shown in figure 1.7.

Table 1.3: Cohort characteristics of the PanCareSurFup cohort.

	Five-year Survivors	%
Overall	69,460	100.0
Sex		
Male	37,738	54.3
Female	31,722	45.7
Age at Diagnosis		
<5 years	26,969	38.8
5–9 years	15,587	22.4
10–14 years	15,423	22.2
15–19 years	11,482	16.5
Decade of Diagnosis		
<1970	8,993	13.0
1970–1979	13,479	19.4
1980–1989	20,900	30.1
1990–1999	19,260	27.7
≥2000	6,828	9.8
Attained Age		
0–19 years	16,397	23.6
20-–29 years	22,329	32.2
30–39 years	17,522	25.2
≥40 years	13,212	19.0
Years from Diagnosis		
5–14 years	23,833	34.3
15–24 years	22,282	32.1
25–34 years	14,087	20.3
35–44 years	6,796	9.8
45+ years	2,462	3.5
Childhood Cancer Diagnosis		
Leukaemia	16,595	23.9
Hodgkin Lymphoma	6,000	8.6
Non-Hodgkin Lymphoma	3,350	4.8
Central Nervous System	14,096	20.3
Neuroblastoma	3,169	4.6
Retinoblastoma	2,578	3.7
Wilms Tumour	4,756	6.9
Bone Sarcoma	3,147	4.5
Soft-Tissue Sarcoma	4,502	6.5
Other	10,905	15.7
Not classifiable	363	0.5

Table 1.4: Period of childhood cancer diagnosis and follow-up for each country contributing to the PanCareSurFup cohort.

Country	Years of Diagnosis	End of Follow-up
France	1946–1986	Sep-14
Hungary	1971–2008	Dec-14
Italy Population-based	1965–2005	May-10
Italy Hospital-based	1960–2007	Dec-12
Netherlands	1963–2001	Dec-12
Denmark	1943–1998	Dec-03
Sweden	1958–1998	Dec-03
Norway	1953–1997	Dec-02
Finland	1953–2006	Dec-11
Iceland	1955–1998	Dec-03
Slovenia	1960–2002	Jul-14
Switzerland	1964–2005	Dec-13
UK	1940–1991	Dec-06

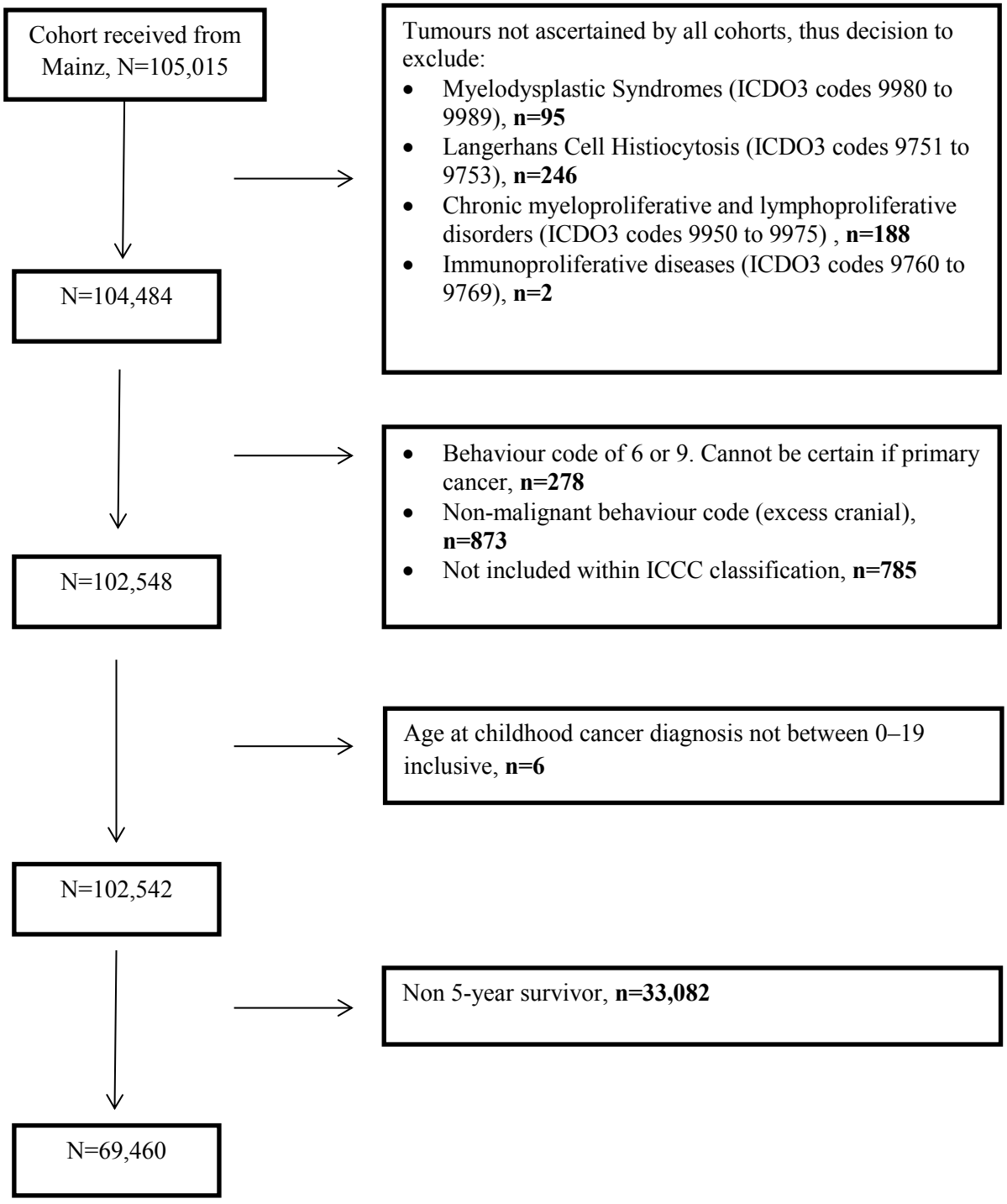


Figure 1.7: Process to create and quality assure PanCareSurFup cohort – performed in Birmingham.

1.5 RATIONALE AND AIMS OF THESIS

Clinical follow-up guidelines are imperative for the long-term survival and care of childhood, teenage and young adult cancer survivors. Although guidelines for the long-term follow-up of childhood cancers exist, there are still some gaps in knowledge and inconsistencies between published guidelines. Thus far there have not been any guidelines published specifically for the long-term care of TYA cancer survivors. Large-scale studies are needed to provide robust estimates of the risk of adverse health outcomes among these cancer populations in order to inform and provide the required evidence for the development and updating of long-term follow-up guidelines. The PanCareSurFup provides the largest cohort of childhood and adolescent cancer survivors in the world thus can be used to develop accurate estimates of the most severe and life-threatening outcomes that arise after treatment for cancer. The TYACSS cohort provides a large population-based cohort that has been linked to several national databases therefore can be used to address the gap in knowledge regarding adverse health outcomes that has been identified as a research priority by the Department of Health, the National Institute for Health and Clinical Excellence and the National Cancer Research Institute[145-147]. The research conducted in this thesis will aid in revising and developing follow-up guidelines, informing survivors and parents, and raising awareness adverse health outcomes faced by childhood, teenage and young adult cancer survivors.

The principal aims of this thesis are five-fold:

1) Investigate which groups of survivors in the TYACSS cohort are at increased risk of developing specific types of SPNs.

2) With the use of the Hospital Episode Statistics (HES) database, investigate which groups of survivors in the TYACSS cohort are at increased risk of being hospitalised for a cerebrovascular event in England.
3) Investigate which subgroups of CNS tumour survivors in the TYACSS cohort are at increased risk of specific causes of death compared to the age- and gender-matched general population.
4) Investigate which subgroups of childhood cancer survivors in the PanCareSurFup cohort are at an increased risk of developing a subsequent primary soft-tissue sarcoma.
5) Investigate which subgroups of childhood cancer survivors in the PanCareSurFup cohort are at an increased risk of developing a subsequent primary breast cancer.

Each of the aforementioned studies was chosen as they investigate the risk of the most serious and life-threatening adverse health outcomes after childhood and TYA cancer. Both subsequent primary neoplasms and cerebrovascular disease contribute substantially to premature mortality among long-term cancer survivors; furthermore these events, in the absence of mortality, can be severely life debilitating. Therefore morbidity rather than mortality was chosen as the focus for these two endpoints. Premature mortality among CNS tumour survivors was chosen as a focus of this thesis due to existing literature[24, 26] and preliminary analyses highlighting that these survivors experience a high risk of premature mortality. The aims of the PanCareSurFup studies were to provide estimates of the risk of developing SPNs in long-term survivors of childhood cancer. This thesis focuses on subsequent breast cancers and soft-tissue sarcoma, as previous literature have shown childhood cancer survivors to have a large risk of these SPNs, however there are gaps in

literature regarding risk of breast cancer after 40 years of age and the risk of specific types of soft-tissue sarcoma.

1.6 FRAMEWORK OF THESIS

The thesis comprises five main chapters which are based on the five aims stated above. Chapters Two to Four are concerned with the adverse health outcomes experienced by survivors within the TYACSS cohort. Chapter Two focuses on the risk of SPNs among TYA cancer survivors in England and Wales. Chapter Three focusses on the risk of hospitalisation for a cerebrovascular event among TYA cancer survivors in England. Chapter Four focusses on the risk of premature mortality and specific causes of death among TYA cancer survivors in England and Wales. Chapters Five and Six are concerned with subsequent primary neoplasms developed among survivors within the PanCareSurFup cohort. Chapter Five focusses on the risk of developing a subsequent primary soft-tissue sarcoma among childhood and adolescent cancer survivors in Europe. Chapter Six focusses on the risk of developing a subsequent primary breast cancer among childhood and adolescent cancer survivors in Europe. To conclude, Chapter seven provides a summary of the main findings and also considers the implications of these findings.

1.7 LITERATURE SEARCH

Pubmed was used as the main source of obtaining relevant scientific papers. Search terms included, but were not limited to, ‘TYA’, ‘teenage and young adult cancer’, ‘AYA’, ‘adolescent and young adult cancer’, ‘childhood cancer’, ‘survivor’, ‘second cancer’, ‘subsequent cancer’, ‘subsequent primary neoplasm’, ‘cardiovascular disease’, ‘strokes’, ‘adverse health outcome’, ‘premature mortality’. Other sources of literature included

bibliographies of relevant papers, attending and gaining knowledge from conferences, websites of known childhood, teenage and young adult cancer survivor cohorts, word of mouth, and discussions with colleagues and peers.

1.8 DECLARATION OF WORK UNDERTAKEN

Dr Raoul Reulen, Professor Mike Hawkins, David Winter, and the PanCareSurFup partners collected the initial data used throughout this thesis. David Winter and myself, performed separate data cleaning exercises to ensure there were no inconsistencies or errors within the data. The cleaning exercises performed by myself are described in the previous sections. I performed all of the statistical analysis, production of results, and drafting of each chapter. My supervisors, Dr Raoul Reulen and Professor Mike Hawkins, provided expert knowledge and proof read all chapters.

Chapter 2

Long-term risks of subsequent primary neoplasms among 200,945 5-year survivors of teenage and young adult cancer

2.1 ABSTRACT

Background: In contrast to survivors of childhood cancer there is very little information addressing the risks of subsequent primary neoplasms (SPNs) experienced after teenage and young adult (TYA) cancer and no previous study has addressed the risks of specific SPNs after specific TYA cancers.

Methods: The Teenage and Young Adult Cancer Survivor Study is a population-based cohort of 200,945 5-year survivors of cancer diagnosed when aged 15-39 years between 1971-2006 in England and Wales. We focus on the absolute excess risks (AER), which provide the excess number of SPNs observed per 10,000 survivors per year.

Results: Overall, 12,321 SPNs were diagnosed in 11,565 survivors; most frequently among survivors of breast, cervical, testicular cancer, and Hodgkin lymphoma. For the first time we provide excess risks of specific types of SPNs after each of 17 types of TYA cancer. The excess number of SPNs observed increased with increasing years from diagnosis after each TYA cancer investigated, both in relation to SPNs overall and each specific SPN site potentially directly irradiated. Those surviving beyond 30 years from diagnosis of breast, testicular, cervical cancer and Hodgkin lymphoma experienced the following excess number of SPNs. Breast cancer survivors experienced 29 excess cancers overall; lung accounted for 45% of this. Cervical cancer survivors experienced 47 excess cancers overall; lung, colorectal, and bladder accounted for 82% of this. Testicular cancer survivors experienced 127 excess cancers overall; prostate, bladder, colorectal and lung accounted for 61% of this. Among Hodgkin lymphoma survivors, women experienced 169 excess cancers overall, breast and lung accounted for 58% of this; men experienced 123 excess cancers overall, lung accounted for 41% of this.

Conclusion: We provide long-term excess numbers of the more common specific SPNs developing after specific types of TYA cancer, which gives an evidence-base for planning surveillance for SPNs in long-term follow-up clinics.

2.2 INTRODUCTION

Survival from cancer diagnosed in teenagers and young adults (TYA) has improved, currently 5-year relative survival in Europe is 82%[11]. Survivors are at risk of developing serious morbidities, including subsequent primary neoplasms (SPNs). The risk overall has been estimated to be between 1.5- and 3.1-fold that expected from the general population[7, 29], but previous cohorts were small.

Previous research regarding the development of SPNs among survivors of TYA cancers has concentrated on the risk after the most common cancers such as lymphomas, testicular cancer, and breast cancer[33, 34, 36, 38, 54, 60, 149-151]. Only one study has comprehensively investigated the risk of developing any SPN after each TYA cancer, but the risks of specific types of SPN were not investigated[29]. It is anticipated that principal factors determining the risks of SPNs will relate to types and doses of TYA cancer treatments. TYA cancer treatment varies greatly by cancer type and therefore in the absence of detailed treatment information it is essential to investigate the risk of specific SPNs after specific types of TYA cancer. Such risk stratification information is necessary for the development of evidence-based long-term clinical follow-up guidelines. In contrast to survivors of childhood cancer there is very little literature currently available which addresses SPN risks after the entire spectrum of specific TYA cancers.

The main aims of this large-scale population-based study were to: 1) provide risks of all and specific types of SPN after each type of TYA cancer; 2) explore variation in such risks with years from diagnosis, age at diagnosis, decade of diagnosis, and gender where sufficient numbers were available.

2.3 METHODS

2.3.1 Teenage and Young Adult Cancer Survivor Study (TYACSS)

The TYACSS is a large population-based cohort consisting of 200,945 5-year survivors of cancer diagnosed aged 15-39 years between 1971-2006 in England and Wales. It was ascertained from the Office for National Statistics and the Welsh Cancer Registry. Ethical approval was provided by the National Research Ethics Service (ref: 16/LO/0895) and permission to process information without individual consent by the National Information Governance Board (NIGB) for Health and Social Care (ref: 3-03(c)2010). First primary neoplasms (FPNs) were grouped according to the internationally acknowledged classification scheme for tumours diagnosed in adolescence and young adulthood (see Table 2.1)[13]. Carcinomas and germ cell tumours were further subdivided by anatomical site because the implications of treatment for the risk of SPN will vary depending on site of treatment. We aimed to produce risk estimates after each specific FPN therefore survivors of the 3,118 'other' cancers were not included, resulting in 197,827 5-year survivors (See Table 2.2 for types of `other` cancers).

2.3.2 Ascertainment of subsequent primary neoplasms

Individual patient record linkage with NHS-Digital provided notification of vital status, date of death, date of emigration and when an individual developed a SPN, the anatomical site and

date of this neoplasm. Cancer registrations were classified as a SPN according to the International Association of Cancer Registries (IACR) and International Agency for Research on Cancer (IARC) rules for defining multiple primary tumours using the IACR/IARCtools software[152]. To ensure that potential SPNs were not a recurrence of the original TYA cancer, SPNs occurring in the same or neighbouring anatomical sites as the FPN were excluded (see Table 2.3 for exclusions).

Tumours of the central nervous system (CNS) including meningiomas and bladder neoplasms were included in all analyses irrespective of histological tumour classification (malignant, benign, or uncertain).

2.3.3 Statistical analysis

Individuals were followed from date of 5-year survival from diagnosis of their TYA cancer until the first occurrence of death, emigration, or study end date (31st December 2012). To avoid bias multiple SPNs per individual were allowed for all comparisons with expected numbers from the general population. For the cumulative incidence the first SPN only was considered.

Standardised incidence ratios (SIRs) were calculated as the observed divided by the expected number of neoplasms. Absolute excess risks (AERs) were calculated as the observed minus expected number of neoplasms, divided by the person-years at risk and multiplied by 10,000. We often report the excess number of cancers without specifying the underlying person-years at risk because this is always per 10,000 person-years. The expected number of neoplasms was derived from multiplying the number of person-years accrued, stratified by sex, attained

age (five-year bands) and calendar year (one-year bands), by the corresponding cancer rate in the general population of England and Wales and then summing appropriately. For those TYA cancers with 200 or more observed SPNs (Table 2.4), SIRs were provided by specific type of SPN (Table 2.5). In the Results and Discussion we restrict attention to FPN/SPN combinations with at least 100 SPNs and a statistically significant SIR (highlighted in red in Table 2.5).

AERs were calculated stratified by years from diagnosis, age at diagnosis, decade of diagnosis, and sex where there were at least 100 SPNs. To explore the simultaneous effect of these explanatory factors, multivariable Poisson regression incorporating the expected number of events was used to derive relative excess risks (RER) [153, 154]. RERs can be interpreted as the ratio of AERs adjusted for other potential explanatory factors included within the statistical model. AERs by an explanatory factor were reported in the Results and Discussion if the trend in both the AERs and RERs were each statistically significant and the difference in the AERs between the lowest and highest level of the risk factor was at least 9 excess SPNs per 10,000 person-years. A two-sided p-value <0.05 was considered statistically significant for all analyses. All analyses were conducted in Stata version 14.1.

2.4 RESULTS

2.4.1 Cohort characteristics

Within the follow-up period, 12,321 SPNs were diagnosed in 11,565 of the 197,827 survivors in the cohort. SPNs were most frequently observed among survivors of breast cancer (n=1877), cervical cancer (n=1675), Hodgkin lymphoma (n=1606), and testicular cancer (n=1435) (Table 2.4). Investigation of all FPN/SPN combinations with at least 100 SPNs

revealed that neither age at diagnosis nor decade of diagnosis was systematically associated with both the AERs and RERs (as specified above for reporting) except for breast cancer after Hodgkin lymphoma in women (Table 2.6), and lung cancer after Hodgkin lymphoma in men (Table 2.7). In the remainder of the Results we consider only variation of AERs and RERs with years from diagnosis, in addition to these two findings (Table 2.8).

2.4.2 SPN after breast cancer in women

Among breast cancer survivors, women had 1.8-times the expected risk of developing a SPN (SIR=1.8, 95% confidence interval [CI]=1.7-1.8) corresponding to 20 excess SPNs (AER=19.5, CI=17.4-21.5) (Table 2.4). Statistically significant SIRs related to ovarian, lung, corpus uteri, other genital, melanoma, and colorectal cancer and were 2.8 (CI=2.5-3.1), 2.3 (CI=2.1-2.6), 2.1 (CI=1.8-2.4), 1.4 (CI=1.1-1.6), 1.2 (CI=1.004-1.5), and 1.2 (CI=1.023-1.4) respectively (Table 2.5). The total AER increased from 12 at 5-9 years from diagnosis to 29 beyond 30 years from diagnosis (multivariable $P_{trend}<0.001$); the AER for lung cancer also increased with years from diagnosis (multivariable $P_{trend} <0.001$) (Table 2.8). Among patients who had survived at least 30 years since their diagnosis, lung cancer accounted for 13 (45%) of the total number of excess neoplasms. The cumulative incidence of lung at 35 years from diagnosis was 2.9% (CI=2.5-3.2), whereas 2.0% was expected (Figure 2.1).

2.4.3 SPN after cervical cancer

Cervical cancer survivors had 1.3-times the expected risk of developing a SPN (SIR=1.3, CI=1.2-1.3), corresponding to 10 excess SPNs (AER=10.2, CI=8.0-12.4) (Table 2.4). Significant excess SIRs related to bladder (SIR=4.3, CI=3.5-5.1), lung (SIR=2.9, CI=2.6-3.2) and colorectal cancer (SIR=2.1, CI=1.8-2.3) (Table 2.5). There was a significant deficit in the

SIR related to breast cancer (SIR=0.7, CI=0.7-0.8) were likely related to treatment-induced menopause. The total AER increased from 7 at 5-9 years from diagnosis to 47 subsequent to 30 years from diagnosis (multivariable P_{trend} <0.001) (Table 2.8). The AER for each of lung, colorectal, and bladder neoplasms increased with years from diagnosis (each multivariable P_{trend} <0.001). Among patients who had survived at least 30 years since their diagnosis, lung, colorectal, and bladder cancer accounted for 17 (37%), 11 (23%) and 10 (22%) of the total number of excess neoplasms, respectively. The cumulative incidence of subsequent lung, colorectal, and bladder neoplasms at 35 years from diagnosis were 3.6% (CI=3.2-4.2), 2.6% (CI=2.2-3.0), and 1.3% (CI=1.0-1.6); whereas 1.6%, 1.5%, and 0.4% were expected, respectively (Figure 2.1).

2.4.4 SPN after testicular cancer

Testicular cancer survivors had 1.8-times the expected risk of developing a SPN (SIR=1.8, CI=1.7-1.9), corresponding to 19 excess SPNs (AER=18.9, CI=16.6-21.1) (Table 2.4). Specific sites with significant SIRs related to bladder, colorectal, lung, and prostate SPNs were 2.7 (CI=2.3-3.2), 1.9 (CI=1.6-2.2), 1.5 (CI=1.3-1.7), and 1.4 (CI=1.2-1.6), respectively (Table 2.5). The total AER increased significantly from 4 at 5-9 years from diagnosis to 127 subsequent to 30 years from diagnosis (multivariable P_{trend} <0.001) (Table 2.8). The AER for each of bladder, colorectal, lung, and prostate increased with years from diagnosis (each multivariable P_{trend} <0.001). Among patients who had survived at least 30 years since their diagnosis, prostate, bladder, colorectal and lung cancers accounted for 25 (20%), 23 (18%), 20 (15%) and 10 (8%) of the total excess number of neoplasms, respectively. The cumulative incidence of bladder and colorectal neoplasms at 35 years from diagnosis were 2.9% (CI=2.4-3.6) and 3.0% (CI=2.5-3.6); whereas 1.1% and 1.8% were expected, respectively (Figure 2.1).

2.4.5 SPN after Hodgkin lymphoma in women

Among Hodgkin lymphoma survivors, women were at 3.1-times the expected risk of developing a SPN (SIR=3.1, CI=2.9-3.3), corresponding to 56 excess neoplasms (AER=55.7, CI=50.4-61.1) (Table 2.4). Significant SIRs related to breast (SIR=3.2, CI=2.9-3.5) and lung (SIR=5.3, CI=4.3-6.5) (Table 2.5). The total AER increased significantly from 8 at 5-9 years from diagnosis, to 169 beyond 30 years from diagnosis (multivariable P_{trend} <0.001); the AER for breast and lung cancer also increased with years from diagnosis (each multivariable P_{trend} <0.001) (Table 2.8). Among patients who had survived at least 30 years since their diagnosis, breast and lung cancers accounted for 72 (43%) and 26 (15%) of the total excess number of neoplasms, respectively. The number of excess breast cancers observed declined significantly with increasing age at diagnosis (multivariable P_{trend} <0.001) (Table 2.6). Those diagnosed at ages 15-19 and 35-39 years experienced 54 and 9 excess breast cancers, respectively. The cumulative incidence of breast and lung neoplasms at 35 years from diagnosis were 14.4% (CI=12.9-15.9) and 3.8% (CI=3.0-4.8); whereas 4.9% and 0.9% were expected, respectively (Figure 2.1).

2.4.6 SPN after Hodgkin lymphoma in men

Among Hodgkin lymphoma survivors, men were at 2.6-times the expected risk of developing a SPN (SIR=2.6, CI=2.4-2.8) corresponding to 30 excess neoplasms (AER=29.9, CI=26.3-33.6) (Table 2.4). The SIR for lung neoplasms was significantly increased (SIR=4.8, CI=4.1-5.5) (Table 2.5). The total AER increased significantly from 6 at 5-9 years from diagnosis to 122 beyond 30 years from diagnosis (multivariable P_{trend} <0.001) (Table 2.8). The AER for lung cancer also significantly increased with years from diagnosis (multivariable P_{trend} <0.001). Among men who had survived at least 30 years since their diagnosis, lung cancer

accounted for 50 (41%) of the total number of excess neoplasms. The excess number of lung cancers observed decreased significantly with more recent decade of diagnosis (1971-2006) (multivariable P_{trend} <0.001) (Table 2.7). The AER for lung cancer for survivors of Hodgkin lymphoma diagnosed in 1971-1979 was 19 compared to 1 among those diagnosed 1990-2006. The cumulative incidence of lung neoplasms was 5.1% (CI=4.3-6.0) at 35 years from diagnosis, whereas 1.4% was expected (Figure 2.1).

2.4.7 SPN after thyroid cancer in women

Among thyroid cancer survivors, women were at 1.4-times the expected risk of developing a SPN (SIR=1.4, CI=1.2-1.5) corresponding to 13 excess neoplasms (AER=13.1, CI=8.4-17.8) (Table 2.4). The SIR of breast neoplasms was significantly increased (SIR=1.3, CI=1.1-1.5) (Table 2.5). The total AER increased significantly from 5 at 5-9 years from diagnosis to 22 beyond 30 years from diagnosis (multivariable P_{trend} =0.048) (Table 2.8).

2.4.8 SPN after other specific FPNs

A significant deficit in the SIR was found for breast cancer after ovarian cancer (SIR=0.8, CI=0.6-0.9) (Table 2.5). Oophorectomy reduces circulating oestrogens and progesterones; such hormones are important in the development of hormone dependent breast cancers[155].

FPN/SPN combinations with between 25 and 99 observed SPNs and a SIR of at least 5 which was statistically significant are also highlighted in blue in Table 2.5.

2.5 DISCUSSION

For the first time we provide excess risks of specific types of SPNs after each of 17 types of TYA cancer. There has previously been only one study which addressed the risk of all SPNs combined after each TYA cancer but no study has previously considered specific SPNs. We have almost double the number of SPNs and an additional million person-years of follow-up compared to this previous study and thus we are in an unprecedented position to address the risks of specific types of SPN after each type of TYA cancer. Previous studies investigating the risk of SPNs with years from diagnosis have focused on the SIR, a measure of multiplicative risk which relates to an arbitrary baseline risk and is therefore difficult to interpret. We concentrated on the AER, which is the excess number of observed SPNs beyond those expected from the general population and so is directly interpretable in terms of adverse health impact on survivors. To our knowledge we are the first to provide AERs by years from diagnosis for specific TYA cancers other than for Hodgkin lymphoma.

Younger age at radiation exposure is a risk factor for the development of breast cancer among many populations exposed to radiation, including atomic bomb survivors, tuberculosis patients monitored with X-rays, children with benign disorders treated with radiotherapy, and childhood cancer survivors treated with chest radiotherapy[55-57, 156]. Thus, the age at diagnosis/treatment effect of breast cancer after Hodgkin lymphoma in our cohort is not entirely surprising. Among childhood cancer survivors, age at diagnosis/treatment is an important risk factor—younger age at treatment is associated with an increased risk of developing an SPN, particularly radiation-induced SPNs [97, 102]. This *could* be due to increased susceptibility of tissues to mutagenesis at younger ages or genetic susceptibility[157]. These potential causes, are less likely to affect TYA cancer survivors (exception of breast tissue),

and could explain the lack of age at diagnosis/treatment effect on the risk of SPNs. However, this is the first study to investigate how the risk of developing a SPN varies within the TYA age range, thus further studies are required to confirm this lack of effect.

Knowledge of late effects of cancer treatment has resulted in lower radiation exposures for treatments of good prognosis cancers in recent years[158, 159], however the multivariable regression revealed that the risk of developing a SPN did not vary with decade of diagnosis with the exception of lung cancer after Hodgkin lymphoma in men. So at present there is no evidence that attempts to reduce the risk of SPNs among more recently treated TYA cancer survivors is having a detectable impact so far.

2.5.1 SPN after breast cancer in women

The SIRs which we report were broadly consistent with previous literature restricted to younger age groups[34, 149-151]. The increased risk of ovarian cancer could relate to shared genetic and hormonal risk factors (e.g. BRCA1/2 mutations)[160]. The increased risk of uterine cancers may relate to tamoxifen used to treat the breast cancer—a previous large case-control study found that risk of uterine cancer increases with duration of tamoxifen treatment[161]. Among the 6 anatomical sites at which an excess of SPNs was observed, only the lungs would be directly exposed if external-beam radiotherapy was used to treat the breast cancer. A previous large case-control study observed a dose-response relationship between radiation therapy and lung cancer risk among breast cancer survivors diagnosed at any age (not TYA specific)[32]. Of the 6 sites with an excess of SPNs, it was only for lung cancer that the AER increased with increasing years from diagnosis. Among patients who had survived at least 30 years since their diagnosis, lung cancer accounted for 13 (45%) of the total number of excess

neoplasms. Smoking is an important risk factor for lung cancer, and the risk of lung cancer following radiation for breast cancer has been reported to be increased among smokers[32]. Smoking could contribute to the increased risk of lung cancer observed among breast cancer survivors in this study. In terms of evidence for long-term clinical surveillance of survivors of TYA breast cancer clearly lung cancer should be of principal concern and late effects follow-up clinics should concentrate on effective counselling and smoking cessation advice.

2.5.2 SPN after cervical cancer

Among survivors of TYA cervical cancer there were over twice the expected numbers of bladder, lung, and colorectal cancer. The bladder and bowel would be directly exposed if external-beam radiotherapy was used to treat the cervical cancer. A large case-control study observed a dose-response relationship with radiotherapy and the risk of both bladder and rectal cancers among cervical cancer survivors[162]. The increased risk of lung cancer may be associated with smoking as both cervical cancer and smoking are more prevalent in lower socioeconomic groups[163, 164]. Furthermore previous studies have observed that cervical cancer survivors are more likely to smoke than the general population of the same age[165]. The AER increased with increasing years from diagnosis for lung, colorectal and bladder cancers. Among patients who had survived at least 30 years since their diagnosis, lung, colorectal, and bladder cancers accounted for 17 (37%), 11 (23%), and 10 (22%) of the total number of excess neoplasms, respectively—in aggregate accounting for 82% of the total number of excess neoplasms. Long-term clinical surveillance of survivors of TYA cervical cancer should concentrate on potential cancers of lung, bowel, and bladder. In addition, late effect clinics should concentrate on interventions to reduce smoking among cervical cancer survivors.

2.5.3 SPN after testicular cancer

Treatment for testicular cancer may involve irradiating the para-aortic lymph nodes[166] which may explain the excess of SPNs observed in abdominal sites (prostate, bladder and colorectal). The excess of SPNs observed in the abdomen is consistent with international studies of testicular cancer survivors[33, 35, 41, 60]. The excess of lung SPNs may be due to radiotherapy to the lungs, previous studies have observed an increased risk of lung cancer among survivors of testicular cancer who were given chest radiotherapy[53, 60]. The AERs increased with increasing years from diagnosis for prostate, bladder, colorectal and lung cancer. Among patients who had survived at least 30 years since their diagnosis, prostate, bladder, colorectal, and lung cancer accounted for 25 (20%), 23 (18%), 20 (15%) and 10 (8%) of the total number of excess neoplasms—in aggregate accounting 61% of the total excess number. Long-term clinical surveillance of survivors of TYA testicular cancer should concentrate on potential prostate, bladder, colorectal and lung cancers.

2.5.4 SPN after Hodgkin lymphoma in women

The high numbers of excess breast and lung neoplasms observed is consistent with previous literature and is most likely caused by direct chest radiotherapy to treat the Hodgkin lymphoma [51-53, 55-57]. An increased susceptibility of breast tissue to radiation at younger ages might be the cause of the increased number of excess breast SPNs among survivors diagnosed at younger ages[54]. Our findings are consistent with previous large-scale studies of Hodgkin lymphoma survivors; for which a substantial amount of literature already exists, and unlike for other TYA cancers considered we have very little to add[31, 36, 38, 54].

2.5.5 SPN after Hodgkin lymphoma in men

Men who had survived Hodgkin lymphoma experienced approximately 5-fold the number of lung cancers expected. The lungs would be directly exposed if external-beam radiotherapy was used to treat the Hodgkin lymphoma; previous studies of Hodgkin lymphoma survivors provided evidence of a dose-dependent increase in lung cancer risk with radiotherapy with/without chemotherapy[51-53]. This study confirms the decrease in lung cancer risk with more recent calendar-period of diagnosis observed in a recent Dutch study of Hodgkin lymphoma survivors (Current study: 1971-2006; Dutch study: 1965-2000)[36]. This may be due to a latency effect where more recently diagnosed survivors simply have not had enough time to develop a lung SPN or due to changes in treatment for Hodgkin lymphoma over recent decades including withholding radiotherapy or irradiating less tissue than in previous decades[159]. However a decrease in lung cancer risk was not observed after Hodgkin lymphoma in women, therefore it is more likely that the decrease in lung cancer among men is due to changes in smoking habits over recent decades. The AER for lung cancer increased with increasing years from diagnosis. Previous studies have reported an increase in the number of excess lung cancers with increasing years from diagnosis[36, 54]; however to our knowledge, we are the first to provide the number of excess lung cancers in men and women separately. Men had twice the number of excess lung cancers (50) than women (26) beyond 30 years from diagnosis. Among men who had survived at least 30 years since their diagnosis, lung cancer accounted for 50 (41%) of the total number of excess neoplasms. Evidence-based long-term clinical surveillance for SPNs after Hodgkin lymphoma in men should concentrate on potential lung cancers and long-term clinical follow-up should advise survivors not to smoke.

2.5.6 Strengths and limitations

Strengths of our cohort study relate to its large-scale and population-based design with the inclusion of all 5-year survivors in England and Wales. A limitation of using cancer registrations is the lack of detailed treatment information; however we have provided risk estimates for specific TYA cancers. Although cancer treatments for specific cancer types have changed over decades during which members of the cohort were treated, the variation in treatments for any specific cancer over these decades is, in general, appreciably less than variation in treatments between specific cancers.

There is a possibility that recurrence or metastases of the TYA cancer could have been mistaken for a SPN. However we used the IACR/IARC rules to define multiple primary cancers and further excluded any additional neoplasms at the TYA cancer site. By using these criteria we excluded any contralateral SPNs such as breast or testicular SPNs. Therefore we provide a conservative estimate of the risk of specific SPNs after specific TYA cancers, and although many of the estimates we report are substantial they are likely to be an underestimate of the true risk. Also we were mindful of the common sites of metastatic spread for specific FPNs when interpreting the SPNs observed and commented on this possibility where we considered it appropriate.

Smoking is an important risk factor for lung cancer, however we did not have information on smoking status of survivors therefore were unable to determine how much of the excess lung cancers observed were caused by smoking.

2.6 CONCLUSIONS

For the first time we provide the excess risks of specific SPNs after each of 17 types of TYA cancer. This study demonstrates for the first time that the excess number of SPNs observed increased with increased period of follow-up from diagnosis after each TYA cancer investigated. Furthermore for each specific SPN site which would have been directly irradiated if external-beam radiotherapy was used to treat the original TYA cancer comparable relationships were observed. Among patients who had survived at least 30 years since their diagnosis of cervical cancer, testicular cancer, Hodgkin lymphoma in women, breast cancer, and Hodgkin lymphoma in men, we have identified just a small number of specific SPNs which account for 82%, 61%, 58%, 45% and 41% of the total excess number of neoplasms, respectively. This is a considerable advance on existing knowledge and provides an initial basis for developing evidence-based long-term clinical follow-up guidelines for this understudied group of survivors.

Table 2.1: Groupings of TYA cancer based on the adolescent and young adult cancer classification scheme. (Refinements are highlighted in red)

Broader Groupings used in current study	AYA classification	AYA code
Leukaemia	Acute Lymphoid Leukaemia	1.1
	Acute Myeloid Leukaemia	1.2
	Chronic Myeloid Leukaemia	1.3
	Other and Unspecified Leukaemias	1.4
Non-Hodgkin Lymphoma	Non- Hodgkin Lymphoma, specified subtype	2.1.1
	Unspecified Non-Hodgkin Lymphoma	2.1.2
	Myeloma, mast cell tumours and miscellaneous lymphoreticular neoplasms NEC	9.2.3
Hodgkin Lymphoma	Hodgkin Lymphoma, specified subtype	2.2.1
	Hodgkin lymphoma NOS	2.2.2
Brain	Pilocytic Astrocytoma	3.1.1
Pituitary Gland	Other specified low grade astrocytic tumours	3.1.2
Meninges	Glioblastoma and anaplastic astrocytoma	3.1.3
Spinal Cord & other CNS	Astrocytoma, NOS	3.1.4
	Oligodendroglioma	3.2.1
	Other specified glioma	3.2.2
	Glioma, NOS	3.2.3
	Ependymoma	3.3
	Medulloblastoma	3.4.1
	Supratentorial PNET	3.4.2
	Craniopharyngioma	3.5.1
	Other pituitary tumours	3.5.2
	Pineal tumours	3.5.3
	Choroid plexus tumours	3.5.4
	Meningioma	3.5.5
	Nerve sheath tumours of CNS	3.5.6
	Other specified intracranial and intraspinal neoplasms	3.5.7
	Unspecified malignant intracranial and intraspinal neoplasms	3.6.1
	Unspecified benign and borderline intracranial and intraspinal neoplasms	3.6.2
	Germ cell intracranial	6.2.1
Bone Neoplasms	Osteosarcoma	4.1
	Chondrosarcoma	4.2
	Ewing sarcoma of bone	4.3.1
	Ewing sarcoma of specified site other than bone	4.3.2
	Ewing sarcoma of unspecified site	4.3.3
	Other specified bone tumours	4.4.1
	Unspecified bone tumours	4.4.2

Soft Tissue Sarcoma	Fibrosarcoma	5.1.1
	Malignant Fibrous Histiocytoma	5.1.2
	Dermatofibrosarcoma	5.1.3
	Rhabdomyosarcoma	5.2
	Liposarcoma	5.3.1
	Leiomyosarcoma	5.3.2
	Synovial sarcoma	5.3.3
	Clear cell sarcoma	5.3.4
	Blood vessel tumours	5.3.5
	Nerve sheath tumours	5.3.6
	Alveolar soft part sarcoma	5.3.7
	Other specified	5.3.8
	Unspecified soft tissue sarcoma	5.4
Melanoma	Melanoma	7.1
Carcinomas – by site		8
Thyroid	Thyroid Carcinoma	8.1
Head and Neck	Nasopharyngeal carcinoma	8.2.1
	Other sites in lip, oral cavity and pharynx	8.2.2
	Nasal cavity, middle ear, sinuses, larynx and other and ill-defined head and neck	8.2.3
Lung	Trachea, bronchus and lung	8.3
Breast	Carcinoma of breast (women only)	8.4
Bladder	Carcinoma of bladder	8.5.2
	Unspecified malignant neoplasms, NEC (in bladder site)	10
	Unspecified benign and borderline neoplasms, NEC (in bladder site)	Not in AYA
	Benign and borderline neoplasms of bladder (ICDO3 code 8010-8589, 8982)	Not in AYA
GU Tract (other)	Carcinoma of kidney	8.5.1
	Carcinoma of other and ill-defined sites in GU tract	8.5.5
	Wilms tumour	9.1.1
Ovary	Carcinoma of ovary	8.5.3
	Germ cell and trophoblastic neoplasms of gonads (women only)	6.1
	Other specified gonadal tumours (women only)	9.2.2
Cervix	Carcinoma of cervix	8.5.4
Gastrointestinal Tract	Carcinoma of colon and rectum	8.6.1

	Carcinoma of stomach	8.6.2
	Carcinoma of liver and intrahepatic bile ducts	8.6.3
	Carcinoma of pancreas	8.6.4
	Carcinoma of other and ill-defined sites in GI tract	8.6.5
Testis	Germ cell gonadal (men only)	6.1
	Other specified gonadal tumours (men only)	9.2.2
Other	Other non-gonadal sites	6.2.2
	Non melanoma skin cancer (non-epithelial tumours only)	7.2
	Carcinoma of breast (men only)	8.4
	Adrenocortical carcinoma	8.7.1
	Carcinoma of other and ill-defined sites, NEC	8.7.2
	Neuroblastoma	9.1.2
	Other paediatric and embryonal, NEC	9.1.3
	Paraganglioma and glomus	9.2.1
	Other specified neoplasms, NEC	9.2.4
	Unspecified malignant neoplasms, NEC	10

Abbreviations: AYA= adolescents and young adults; NEC=not elsewhere classified; NOS= not otherwise specified; GI= gastrointestinal; GU=genitourinary; CNS= central nervous system; PNET= primitive neuroectodermal tumour.

Table 2.2: Description of 'Other' TYA cancers excluded from analysis.

Description	Number of SPNs
CNS tumour (located outside of the CNS)	62
Germ cell neoplasm (non-gonadal, extracranial)	607
Non-epithelial Skin Cancer	192
Breast neoplasm in men	103
Adrenocortical carcinoma	82
Carcinoma of other and ill-defined sites, NEC	528
Neuroblastoma	59
Other paediatric and embryonal neoplasms, NEC	63
Paraganglioma and glomus neoplasms	143
Other specified neoplasms, NEC	664
Unspecified malignant neoplasm, NEC	615
Total	3,118

Abbreviations: SPNs – subsequent primary neoplasms, CNS – central nervous system, NEC – not elsewhere classified

Table 2.3: Exclusions of TYA cancer and subsequent primary neoplasms combinations

Subsequent Primary Neoplasms	**First Primary Neoplasm**											
	Breast (women)	**Testis**	**Cervix**	**Melanoma**	**Hodgkin lymphoma**	**NHL**	**Thyroid**	**Brain**	**Colorectal**	**STS**	**Ovary**	**Leukaemia**
Breast (women)	Excluded	N/A										
Corpus Uteri			Excluded								Excluded	
Ovary		N/A	Excluded								Excluded	
Other Genital (women)		N/A	Excluded								Excluded	
Kidney												
Bladder												
Other Urinary												
Prostate	N/A		N/A								N/A	
Other Genital (men)	N/A	Excluded	N/A								N/A	
Colorectal									Excluded			
Oesophagus												
Stomach												
Pancreas												
Other Digestive[1]												
Lung & Bronchus												
Other Respiratory												
Melanoma				Excluded								
Brain								Excluded				
Meninges												
Spinal Cord & other CNS												
Pituitary Gland												
Thyroid							Excluded					
STS										Excluded		
Bone Sarcoma										Excluded		
NHL					Excluded	Excluded						Excluded
Leukaemia					Excluded	Excluded						Excluded
Oral												
Other												
--Hodgkin lymphoma					Excluded	Excluded						Excluded
--Other lymphoid					Excluded	Excluded						Excluded
--Eye				Excluded								
--Breast (Men only)	N/A											
--Other Endocrine												

Table 2.3: continued

Subsequent Primary Neoplasms	First Primary Neoplasms										
	Bladder	**Pituitary gland**	**Head & Neck**	**Lung**	**Other Genital (women)**	**Spinal Cord and Other CNS**	**Other Digestive**	**Meninges**	**Urinary (other)**	**Bone Tumour**	**Other Genital (men)**
Breast (women)											N/A
Corpus Uteri					Excluded						N/A
Ovary					Excluded						N/A
Other Genital (women)					Excluded						N/A
Kidney	Excluded								Excluded		
Bladder	Excluded								Excluded		
Other Urinary	Excluded								Excluded		
Prostate					N/A						Excluded
Other Genital (men)					N/A						Excluded
Colorectal											
Oesophagus							Excluded				
Stomach							Excluded				
Pancreas							Excluded				
Other Digestive							Excluded				
Lung & Bronchus				Excluded							
Other Respiratory			Excluded[2]	Excluded							
Melanoma											
Brain											
Meninges								Excluded			
Spinal Cord & other CNS						Excluded					
Pituitary Gland		Excluded									
Thyroid											
STS										Excluded	
Bone Sarcoma										Excluded	
NHL											
Leukaemia											
Oral			Excluded								
Other											
--Hodgkin lymphoma											
--Other lymphoid											
--Eye											
--Breast (Men only)					N/A						
--Other Endocrine											

Abbreviations: NHL – non Hodgkin lymphoma, STS – soft tissue sarcoma, CNS – central nervous system.

[1] All liver subsequent primary neoplasms were excluded because of substantial likelihood of metastatic spread.

[2]Nasal cavity, middle ear, accessory sinuses and larynx excluded only. Trachea, lung and bronchus not exclude

Table 2.4: Risk of any subsequent primary neoplasm after specific types of TYA cancer

First Primary Neoplasm	Total number of SPNs	Women			Men		
		O/E	SIR (95% CI)	AER (95% CI)	O/E	SIR (95% CI)	AER (95% CI)
Breast (women)	1877	1877/1069.6	1.8 (1.7,1.8)	19.5 (17.4,21.5)	-	-	-
Cervix	1675	1675/1307.0	1.3 (1.2,1.3)	10.2 (8.0,12.4)	-	-	-
Hodgkin Lymphoma	1606	903/288.2	3.1 (2.9,3.3)	55.7 (50.4,61.1)	703/271.9	2.6 (2.4,2.8)	29.9 (26.3,33.6)
Testicular	1435	-	-	-	1435/807.6	1.8 (1.7,1.9)	18.9 (16.6,21.1)
Melanoma	981	751/665.7	1.1 (1.0,1.2)	4.5 (1.6,7.3)	230/195.8	1.2 (1.0,1.3)	4.2 (0.6,7.9)
Colorectal	537	302/170.6	1.8 (1.6,2.0)	32.1 (23.8,40.4)	235/125.0	1.9 (1.6,2.1)	28.9 (21.0,36.8)
Non-Hodgkin Lymphoma	511	216/149.5	1.4 (1.3,1.7)	14.8 (8.4,21.2)	295/163.4	1.8 (1.6,2.0)	18.6 (13.8,23.4)
Thyroid	473	397/288.8	1.4 (1.2,1.5)	13.1 (8.4,17.8)	76/55.0	1.4 (1.1,1.7)	10.2 (1.9,18.4)
Soft Tissue Sarcoma	400	255/165.7	1.5 (1.4,1.7)	19.8 (12.9,26.8)	145/106.5	1.4 (1.1,1.6)	9.3 (3.6,15.0)
Ovary	349	349/255.3	1.4 (1.2,1.5)	12.3 (7.5,17.1)	-	-	-
Brain	347	170/104.7	1.6 (1.4,1.9)	17.4 (10.6,24.2)	177/89.7	2.0 (1.7,2.3)	19.1 (13.4,24.7)
Bladder	344	88/87.9	1.0 (0.8,1.2)	0.0 (-8.9,8.9)	256/209.2	1.2 (1.1,1.4)	8.0 (2.6,13.4)
Other Genital (women)*	269	269/141.8	1.9 (1.7,2.1)	37.2 (27.8,46.7)	-	-	-
Leukaemia	234	120/63.3	1.9 (1.6,2.3)	22.9 (14.2,31.5)	114/44.4	2.6 (2.1,3.1)	22.7 (15.9,29.5)
Head & Neck	253	117/87.9	1.3 (1.1,1.6)	12.4 (3.4,21.5)	136/100.3	1.4 (1.1,1.6)	11.6 (4.2,19.0)
Pituitary Gland	220	146/130.2	1.1 (0.9,1.3)	3.9 (-1.9,9.7)	74/65.1	1.1 (0.9,1.4)	3.4 (-3.0,9.7)
Spinal Cord & other CNS	191	95/62.5	1.5 (1.2,1.9)	19.1 (7.9,30.3)	96/44.0	2.2 (1.8,2.7)	30.6 (19.3,41.9)
Meninges	172	116/87.4	1.3 (1.1,1.6)	14.0 (3.7,24.3)	56/29.6	1.9 (1.4,2.5)	25.8 (11.4,40.1)
Urinary(Other)*	139	58/39.0	1.5 (1.1,1.9)	19.1 (4.1,34.1)	81/45.7	1.8 (1.4,2.2)	24.5 (12.2,36.7)
Other Digestive	107	45/30.3	1.5 (1.1,2.0)	19.3 (2.0,36.6)	62/29.5	2.1 (1.6,2.7)	33.9 (17.8,50.1)
Bone Tumour	100	52/32.7	1.6 (1.2,2.1)	14.7 (3.9,25.5)	48/33.1	1.4 (1.1,1.9)	8.1 (0.7,15.6)
Lung	80	38/30.0	1.3 (0.9,1.7)	10.2 (-5.2,25.6)	42/37.4	1.1 (0.8,1.5)	4.4 (-7.8,16.7)
Other Genital (Men)*	21	-	-	-	21/16.8	1.2 (0.8,1.9)	7.2 (-8.2,22.5)

Abbreviations: SPNs-subsequent primary neoplasms, O- observed number of SPNs, E- expected number of SPNs, SIR- standardised incidence ratio, AER-absolute excess risk, CI- confidence interval, CNS-central nervous system

*Other genital cancers in men excludes testis; other genital cancer in women excludes the cervix and ovary; urinary cancer excludes bladder

Table 2.5: Risk of subsequent primary neoplasms after 17 types of TYA cancer * (Blue: between 25-99 observed events, SIR≥5 and statistically significant; Red: ≥100 observed events and SIR statistically significant)

Subsequent Primary Neoplasms	First Primary Neoplasm											
	All[1]		Breast (women only)		Cervix		Testicular		Hodgkin lymphoma (women only)		Hodgkin lymphoma (men only)	
	O/E	SIR (95% CI)	O/E	SIR (95% CI)	O/E	SIR (95% CI)	O/E	SIR (95% CI)	O/E	SIR (95% CI)	O/E	SIR (95% CI)
Breast (women only)	2260/2032.1	1.1 (1.1,1.2)	-	-	532/684.8	0.8 (0.7,0.8)	-	-	431/136.3	3.2 (2.9,3.5)	-	-
Lung & Bronchus	1740/855.8	2.0 (1.9,2.1)	357/152.2	2.3 (2.1,2.6)	335/116.9	2.9 (2.6,3.2)	171/115.5	1.5 (1.3,1.7)	101/19.0	5.3 (4.3,6.5)	198/41.3	4.8 (4.1,5.5)
Colorectal	1290/801.9	1.6 (1.5,1.7)	179/150.2	1.2 (1.0,1.4)[3]	237/115.1	2.1 (1.8,2.3)	206/109.2	1.9 (1.6,2.2)	50/20.2	2.5 (1.8,3.3)	86/39.2	2.2 (1.8,2.7)
Other	793/405.1	2.0 (1.8,2.1)	97/56.7	1.7 (1.4,2.1)	61/46.6	1.3 (1,1.6)	104/52.4	2.0 (1.6,2.4)	37/6.4	5.8 (4.1,8.0)	54/27.7	1.9 (1.5,2.5)
Bladder	606/296.6	2.0 (1.9,2.2)	50/38.6	1.3 (1.0,1.7)	126/29.6	4.3 (3.5,5.1)	167/61.3	2.7 (2.3,3.2)	11/4.9	2.2 (1.1,4.0)	30/22.0	1.4 (0.9,1.9)
Prostate	545/433.5	1.3 (1.2,1.4)	-	-	-	-	185/133.5	1.4 (1.2,1.6)	-	-	48/45.8	1.0 (0.8,1.4)
Melanoma	500/385.6	1.3 (1.2,1.4)	100/81.0	1.2 (1.0,1.5)[4]	61/68.3	0.9 (0.7,1.1)	68/44.4	1.5 (1.2,1.9)	29/17.1	1.7 (1.1,2.4)	20/16.8	1.2 (0.7,1.8)
Ovary	447/244.6	1.8 (1.7,2.0)	291/104.9	2.8 (2.5,3.1)	-	-	-	-	16/16.4	1.0 (0.6,1.6)	-	-
Oral	406/215.3	1.9 (1.7,2.1)	44/28.3	1.6 (1.1,2.1)	42/23.2	1.8 (1.3,2.4)	56/40.7	1.4 (1.0,1.8)	21/4.6	4.6 (2.8,7.0)	51/14.8	3.5 (2.6,4.5)
Corpus Uteri	404/214.8	1.9 (1.7,2.1)	204/95.7	2.1 (1.8,2.4)	-	-	-	-	21/12.8	1.6 (1.0,2.5)	-	-
Kidney	371/175.8	2.1 (1.9,2.3)	39/27.9	1.4 (1.0,1.9)	32/22.2	1.4 (1.0,2.0)	53/30.4	1.7 (1.3,2.3)	11/4.0	2.7 (1.4,4.9)	23/11.0	2.1 (1.3,3.1)
Non-Hodgkin Lymphoma	358/290.4	1.2 (1.1,1.4)	79/57.2	1.4 (1.1,1.7)	51/46.0	1.1 (0.8,1.5)	63/46.2	1.4 (1.0,1.7)	-	-	-	-
Brain	317/186.7	1.7 (1.5,1.9)	28/29.4	1.0 (0.6,1.4)	22/24.0	0.9 (0.6,1.4)	26/28.9	0.9 (0.6,1.3)	11/5.4	2.0 (1.0,3.6)	16/11.4	1.4 (0.8,2.3)
Oesophagus	297/158.4	1.9 (1.7,2.1)	46/20.4	2.3 (1.6,3.0)	23/15.6	1.5 (0.9,2.2)	46/29.8	1.5 (1.1,2.1)	26/2.6	10.2 (6.6,14.9)	46/10.7	4.3 (3.2,5.8)
Pancreas	283/162.8	1.7 (1.5,2.0)	34/30.3	1.1 (0.8,1.6)	26/23.0	1.1 (0.7,1.7)	76/20.9	3.6 (2.9,4.6)	13/3.8	3.4 (1.8,5.8)	22/7.5	2.9 (1.8,4.4)
Other Genital (women only)	282/219.7	1.3 (1.1,1.4)	111/82.0	1.4 (1.1,1.6)	-	-	-	-	31/19.8	1.6 (1.1,2.2)	-	-
Stomach	264/147.6	1.8 (1.6,2.0)	32/20.4	1.6 (1.1,2.2)	22/15.2	1.4 (0.9,2.2)	81/25.7	3.2 (2.5,3.9)	7/2.8	2.5 (1.0,5.2)	26/9.4	2.8 (1.8,4.1)
Other Digestive[2]	254/89.7	2.8 (2.5,3.2)	47/18.3	2.6 (1.9,3.4)	31/14.3	2.2 (1.5,3.1)	39/9.6	4.1 (2.9,5.6)	9/2.5	3.5 (1.6,6.7)	12/3.5	3.4 (1.8,6.0)
Thyroid	244/90.8	2.7 (2.4,3.0)	35/20.4	1.7 (1.2,2.4)	20/17.5	1.1 (0.7,1.8)	13/5.4	2.4 (1.3,4.1)	47/5.1	9.2 (6.7,12.2)	26/2.1	12.3 (8.0,18.0)
Leukaemia	229/151.9	1.5 (1.3,1.7)	51/28.4	1.8 (1.3,2.4)	28/22.7	1.2 (0.8,1.8)	39/25.5	1.5 (1.1,2.1)	-	-	-	-
Other Respiratory	217/92.8	2.3 (2.0,2.7)	30/10.4	2.9 (1.9,4.1)	18/8.2	2.2 (1.3,3.5)	31/19.4	1.6 (1.1,2.3)	20/1.5	13.1 (8.0,20.3)	42/7.2	5.9 (4.2,7.9)
Meninges	214/70.8	3.0 (2.6,3.5)	23/16.9	1.4 (0.9,2.0)	8/13.8	0.6 (0.3,1.1)	11/4.2	2.6 (1.3,4.7)	11/3.0	3.7 (1.8,6.5)	**	**

Table 2.5: continued

Subsequent Primary Neoplasms	First Primary Neoplasm											
	Melanoma		Colorectal		Non-Hodgkin Lymphoma		Thyroid		Soft Tissue Sarcoma		Ovary	
	O/E	SIR (95% CI)	O/E	SIR (95% CI)	O/E	SIR (95% CI)	O/E	SIR (95% CI)	O/E	SIR (95% CI)	O/E	SIR (95% CI)
Breast (women only)	359/313.2	1.1 (1.0,1.3)	74/79.3	0.9 (0.7,1.2)	89/70.9	1.3 (1.0,1.5)	170/130.2	1.3 (1.1,1.5)†	88/72.5	1.2 (1.0,1.5)	101/131.1	0.8 (0.6,0.9)
Lung & Bronchus	82/78.1	1.1 (0.8,1.3)	48/38.1	1.3 (0.9,1.7)	83/37.0	2.2 (1.8,2.8)	34/28.4	1.2 (0.8,1.7)	32/27.7	1.2 (0.8,1.6)	54/23.2	2.3 (1.7,3.0)
Colorectal	80/77.5	1.0 (0.8,1.3)	-	-	47/35.4	1.3 (1.0,1.8)	33/28.2	1.2 (0.8,1.6)	46/26.6	1.7 (1.3,2.3)	58/23.0	2.5 (1.9,3.3)
Other	64/42.4	1.5 (1.1,1.9)	31/17.1	1.8 (1.2,2.5)	33/16.7	2 (1.3,2.7)	33/15.2	2.2 (1.4,2.9)	19/14.1	1.3 (0.7,2)	19/9.4	2 (1.1,2.9)
Bladder	27/27.8	1.0 (0.6,1.4)	32/15.5	2.1 (1.4,2.9)	33/16.5	2.0 (1.4,2.8)	11/9.4	1.2 (0.6,2.1)	13/11.2	1.2 (0.6,2.0)	24/6.0	4.0 (2.6,6.0)
Prostate	40/32.9	1.2 (0.9,1.7)	33/27.3	1.2 (0.8,1.7)	35/29.8	1.2 (0.8,1.6)	14/9.1	1.5 (0.8,2.6)	24/17.8	1.4 (0.9,2.0)	-	-
Melanoma	-	-	20/13.7	1.5 (0.9,2.3)	27/17.2	1.6 (1.0,2.3)	25/17.4	1.4 (0.9,2.1)	24/13.2	1.8 (1.2,2.7)	19/13.6	1.4 (0.8,2.2)
Ovary	32/37.7	0.8 (0.6,1.2)	19/10.2	1.9 (1.1,2.9)	11/8.6	1.3 (0.6,2.3)	16/15.8	1.0 (0.6,1.6)	18/9.1	2.0 (1.2,3.1)	-	-
Oral	13/20.8	0.6 (0.3,1.1)	16/8.8	1.8 (1.0,2.9)	31/11.0	2.8 (1.9,4.0)	13/7.0	1.9 (1.0,3.2)	16/7.5	2.1 (1.2,3.5)	10/4.5	2.2 (1.1,4.1)
Corpus Uteri	33/32.6	1.0 (0.7,1.4)	68/9.5	7.2 (5.6,9.1)	8/7.3	1.1 (0.5,2.2)	11/13.5	0.8 (0.4,1.5)	11/8.0	1.4 (0.7,2.5)	-	-
Kidney	31/17.4	1.8 (1.2,2.5)	23/7.7	3.0 (1.9,4.5)	11/8.8	1.3 (0.6,2.2)	10/6.0	1.7 (0.8,3.0)	14/6.2	2.3 (1.2,3.8)	6/4.3	1.4 (0.5,3.0)
Non-Hodgkin Lymphoma	41/32.1	1.3 (0.9,1.7)	19/12.7	1.5 (0.9,2.3)	-	-	13/11.6	1.1 (0.6,1.9)	13/10.8	1.2 (0.6,2.1)	8/9.1	0.9 (0.4,1.7)
Brain	45/18.4	2.4 (1.8,3.3)	21/7.0	3.0 (1.8,4.6)	9/8.8	1.0 (0.5,1.9)	13/6.6	2.0 (1.0,3.4)	13/6.3	2.1 (1.1,3.5)	**	**
Oesophagus	14/14.1	1.0 (0.5,1.7)	12/7.3	1.6 (0.8,2.9)	20/8.0	2.5 (1.5,3.9)	5/4.7	1.1 (0.3,2.5)	5/5.5	0.9 (0.3,2.1)	**	**
Pancreas	19/15.1	1.3 (0.8,2.0)	9/6.9	1.3 (0.6,2.5)	8/6.8	1.2 (0.5,2.3)	6/5.5	1.1 (0.4,2.4)	**	**	9/4.6	1.9 (0.9,3.7)
Other Genital (women only)	25/35.9	0.7 (0.5,1.0)	27/8.1	3.3 (2.2,4.8)	13/8.4	1.5 (0.8,2.6)	16/15.5	1.0 (0.6,1.7)	8/8.6	0.9 (0.4,1.8)	-	-
Stomach	7/13.1	0.5 (0.2,1.1)	14/6.9	2.0 (1.1,3.4)	18/7.3	2.5 (1.5,3.9)	10/4.5	2.2 (1.1,4.1)	13/5.1	2.6 (1.4,4.4)	**	**
Other Digestive[2]	12/8.7	1.4 (0.7,2.4)	48/3.4	13.9 (10.3,18.4)	**	**	9/3.2	2.8 (1.3,5.3)	11/2.8	4.0 (2.0,7.1)	8/2.8	2.8 (1.2,5.6)
Thyroid	21/11.0	1.9 (1.2,2.9)	**	**	12/3.4	3.6 (1.8,6.3)	-	-	9/2.8	3.3 (1.5,6.2)	9/3.6	2.5 (1.1,4.8)
Leukaemia	15/16.7	0.9 (0.5,1.5)	9/6.9	1.3 (0.6,2.5)	-	-	10/6.1	1.7 (0.8,3.0)	9/5.8	1.6 (0.7,3.0)	10/4.6	2.2 (1.1,4.0)
Other Respiratory	12/8.4	1.4 (0.7,2.5)	8/4.4	1.8 (0.8,3.6)	12/5.1	2.4 (1.2,4.1)	9/2.8	3.2 (1.5,6.1)	**	**	**	**
Meninges	9/7.6	1.2 (0.5,2.2)	**	**	7/2.4	2.9 (1.2,6.0)	12/3.0	4.0 (2.0,6.9)	6/2.0	3.0 (1.1,6.5)	6/2.7	2.2 (0.8,4.9)

Table 2.5: continued

Subsequent Primary Neoplasms	First Primary Neoplasm											
	Brain		Bladder		Other genital (women only)		Leukaemia		Head & Neck		Pituitary Gland	
	O/E	SIR (95% CI)	O/E	SIR (95% CI)	O/E	SIR (95% CI)	O/E	SIR (95% CI)	O/E	SIR (95% CI)	O/E	SIR (95% CI)
Breast (women only)	37/47.6	0.8 (0.5,1.1)	29/39.3	0.7 (0.5,1.1)	80/71.2	1.1 (0.9,1.4)	50/30.3	1.6 (1.2,2.2)	44/39.2	1.1 (0.8,1.5)	28/59.3	0.5 (0.3,0.7)
Lung & Bronchus	17/18.9	0.9 (0.5,1.4)	73/45.2	1.6 (1.3,2.0)	29/14.2	2.0 (1.4,2.9)	14/9.9	1.4 (0.8,2.4)	41/23.0	1.8 (1.3,2.4)	9/17.3	0.5 (0.2,1.0)
Colorectal	17/18.8	0.9 (0.5,1.4)	39/39.8	1.0 (0.7,1.3)	65/13.7	4.7 (3.6,6.0)	16/10.5	1.5 (0.9,2.5)	23/21.2	1.1 (0.7,1.6)	14/17.2	0.8 (0.4,1.4)
Other	56/15.7	3.6 (2.6,4.5)	26/19.1	1.4 (0.8,1.9)	15/5.2	2.9 (1.4,4.3)	15/7.3	2.1 (1,3.1)	28/11.6	2.4 (1.5,3.3)	18/10.5	1.7 (0.9,2.5)
Bladder	8/8.3	1.0 (0.4,1.9)	-	-	20/3.6	5.5 (3.4,8.5)	8/4.4	1.8 (0.8,3.6)	14/10.1	1.4 (0.8,2.3)	9/6.9	1.3 (0.6,2.5)
Prostate	15/13.5	1.1 (0.6,1.8)	62/46.4	1.3 (1.0,1.7)	-	-	5/6.1	0.8 (0.3,1.9)	15/19.6	0.8 (0.4,1.3)	10/10.4	1.0 (0.5,1.8)
Melanoma	16/11.1	1.4 (0.8,2.3)	14/13.1	1.1 (0.6,1.8)	6/6.6	0.9 (0.3,2.0)	12/7.3	1.6 (0.8,2.9)	**	**	13/10.4	1.2 (0.7,2.1)
Ovary	**	**	**	**	-	-	**	**	**	**	8/7.0	1.1 (0.5,2.3)
Oral	9/6.0	1.5 (0.7,2.8)	12/10.9	1.1 (0.6,1.9)	7/2.4	2.9 (1.2,5.9)	29/3.7	7.8 (5.2,11.1)	-	-	6/5.2	1.2 (0.4,2.5)
Corpus Uteri	7/4.4	1.6 (0.6,3.3)	**	**	-	-	**	**	7/4.3	1.6 (0.7,3.4)	12/5.7	2.1 (1.1,3.7)
Kidney	61/4.7	13.0 (9.9,16.6)	-	-	4/2.5	1.6 (0.4,4.1)	7/2.8	2.5 (1.0,5.2)	13/4.9	2.6 (1.4,4.5)	10/4.1	2.4 (1.2,4.5)
Non-Hodgkin Lymphoma	11/8.4	1.3 (0.7,2.3)	11/14.0	0.8 (0.4,1.4)	6/5.1	1.2 (0.4,2.6)	-	-	9/8.0	1.1 (0.5,2.1)	7/7.4	0.9 (0.4,1.9)
Brain	-	-	8/8.0	1.0 (0.4,2.0)	5/2.6	1.9 (0.6,4.5)	17/3.3	5.1 (3.0,8.2)	9/4.6	2.0 (0.9,3.7)	19/4.4	4.3 (2.6,6.7)
Oesophagus	**	**	7/9.6	0.7 (0.3,1.5)	5/1.9	2.6 (0.9,6.1)	14/2.2	6.3 (3.4,10.6)	13/4.8	2.7 (1.5,4.7)	**	**
Pancreas	10/3.6	2.8 (1.3,5.1)	11/7.8	1.4 (0.7,2.5)	5/2.8	1.8 (0.6,4.1)	**	**	**	**	7/3.3	2.1 (0.9,4.4)
Other Genital (women only)	7/6.7	1.0 (0.4,2.1)	7/4.1	1.7 (0.7,3.5)	-	-	9/4.2	2.1 (1.0,4.0)	7/4.4	1.6 (0.6,3.3)	11/7.4	1.5 (0.7,2.6)
Stomach	**	**	12/9.0	1.3 (0.7,2.3)	**	**	**	**	**	**	**	**
Other Digestive[2]	**	**	**	**	6/1.7	3.6 (1.3,7.9)	**	**	**	**	**	**
Thyroid	**	**	**	**	5/1.6	3.1 (1.0,7.2)	10/1.7	6.0 (2.9,11.0)	7/1.7	4.2 (1.7,8.7)	**	**
Leukaemia	12/4.6	2.6 (1.3,4.5)	11/8.0	1.4 (0.7,2.5)	**	**	-	-	**	**	8/4.0	2.0 (0.9,4.0)
Other Respiratory	7/2.7	2.6 (1.1,5.4)	9/6.0	1.5 (0.7,2.9)	**	**	**	**	**	**	**	**
Meninges	40/1.5	26.0 (18.6,35.5)	**	**	**	**	13/1.0	13.2 (7.0,22.6)	**	**	20/1.6	12.5 (7.6,19.3)

Abbreviations: O – observed number of SPNs, E- Expected number of SPNs, SIR- standardised incidence ratio, CI-confidence interval, CNS- central nervous system
*excludes potential subsequent primary neoplasms at the same anatomical site as the TYA cancer, represented by '-'
**results not reliable due to small number of SPNS: <5 observed SPNs
[1]Includes all FPNs listed and other genital cancers in men and bone tumours
[2]Consists of 80 small intestine, 62 gallbladder, 77 retroperitoneum and peritoneum and 31 other or unspecified.

[3]Confidence interval to three decimal places was (1.023-1.380)
[4]Confidence interval to three decimal places was (1.004-1.501)
[†]Breast SPNs after thyroid cancer occurred only in women – expected breast cancers in men was zero

Table 2.6: Absolute excess risks (AERs) and relative excess risks (RERs) of subsequent primary breast neoplasms after Hodgkin lymphoma in women by age at diagnosis

	O/E	AER (95% CI)	RER (95% CI)[1]
Overall	431/136.3	26.7 (23.0,30.4)	
Age at Diagnosis			
15-19	132/12.2	54.4 (44.2,64.7)	1.0 (1.0,1.0)
20-24	115/26.2	29.4 (22.4,36.3)	0.5 (0.4,0.7)
25-29	76/31.2	18.1 (11.2,25.0)	0.4 (0.2,0.6)
30-34	63/34.0	15.2 (7.1,23.4)	0.3 (0.2,0.6)
35-39	45/32.6	8.7 (-0.5,17.9)	0.2 (0.1,0.5)
P_{trend}		*<0.001*	*<0.001*

Abbreviations: O – observed number of SPNs, E- Expected number of SPNs, AER- absolute excess risk, CI-confidence interval
[1]From an externally controlled Poisson regression model which contained the following factors: attained age, decade of diagnosis and age at diagnosis.

Table 2.7: Absolute excess risks (AERs) and relative excess risks (RERs) of subsequent primary lung neoplasms after Hodgkin lymphoma in men by decade of diagnosis

	O/E	AER (95% CI)	RER (95% CI)[1]
Overall	198/41.3	10.9 (9.0,12.8)	
Decade of Diagnosis			
1971-1979	110/23.4	18.9 (14.4,23.3)	1.0 (1.0,1.0)
1980-1989	78/14.1	11.9 (8.7,15.1)	0.9 (0.6,1.3)
1990-2006	10/3.9	1.4 (-0.0,2.8)	0.2 (0.1,0.5)
P_{trend}		*<0.001*	*<0.001*

Abbreviations: O – observed number of SPNs, E- Expected number of SPNs, AER- absolute excess risk, CI-confidence interval
[1]From an externally controlled Poisson regression model which contained the following factors: attained age, decade of diagnosis and age at diagnosis.

Table 2.8: Absolute excess risk (AER) of all and specific SPNs after particular FPNs by years from diagnosis, with percentage of total AER contributed by specific SPNs†

First Primary Neoplasm	Subsequent Primary Neoplasm	Years from Diagnosis												Multivariable
		5-9			10-19			20-29			30+			
		O/E	AER	% AER	O/E	AER	% AER	O/E	AER	% AER	O/E	AER	% AER	P_{trend}‡
Breast (women)	Total[1]	371/190.4	11.7	100	730/391.7	19.6	100	581/338.5	34.5	100	195/149.0	29	100	<0.001
	Corpus Uteri	46/9.9	2.3	19.7	100/36.0	3.7	18.9	51/36.8	2.0	5.8	7/12.9	*	*	0.973
	Ovary	74/20.6	3.5	29.9	128/43.0	4.9	25.0	71/31.2	5.7	16.5	18/10.1	4.4	15.2	0.504
	Other Genital	38/30.9	0.5	4.3	50/33.1	1.0	5.1	18/13.7	0.6	1.7	5/4.3	0.4	1.4	0.251
	Colorectal	24/19.8	0.3	2.6	63/51.6	0.7	3.6	65/51.9	1.9	5.5	27/26.9	0.1	0.3	0.125
	Lung	37/14.6	1.5	12.8	112/48.5	3.7	18.9	154/58.6	13.6	39.4	54/30.5	13.1	45.2	<0.001
	Melanoma	30/23.1	0.4	3.4	45/34.0	0.6	3.1	17/18.1	-0.2	-0.6	8/5.8	1.2	4.1	0.566
	Other	122/71.5	3.3	28.2	232/145.5	5.0	25.5	205/128.2	10.9	31.6	76/58.4	9.8	33.8	<0.001
Cervical	Total[2]	241/179.6	7.1	100	618/509.3	9.7	100	609/465.2	27.3	100	207/152.9	46.5	100	<0.001
	Breast	89/104.4	*	*	251/294.6	*	*	157/227.0	*	*	35/58.8	*	*	-
	Bladder	11/2.1	0.8	11.3	40/8.4	2	20.6	52/12.9	5	18.3	23/6.1	10.1	21.7	<0.001
	Colorectal	23/10.4	1.2	16.9	66/37.9	1.8	18.6	110/46.7	8.1	29.7	38/20.0	10.7	23.0	<0.001
	Lung	45/7.3	3.5	49.3	101/34.5	4.2	43.3	137/52.0	10.8	39.6	52/23.2	17.2	37.0	<0.001
	Other	73/55.3	1.6	22.5	160/133.9	1.7	17.5	153/126.6	3.4	12.5	59/44.8	8.5	18.3	0.243
Testicular	Total[3]	124/81.9	3.8	100	378/246.2	9.0	100	605/318.3	46.6	100	328/161.1	127.0	100	<0.001
	Prostate	1/1.4	0.0	0.0	26/20.0	0.4	4.4	79/66.3	2.1	4.5	79/45.7	25.3	19.9	<0.001
	Bladder	9/5.0	0.4	10.5	30/17.4	0.9	10.0	84/25.0	9.6	20.6	44/14.0	22.8	18.0	<0.001
	Colorectal	16/9.4	0.6	15.8	45/33.4	0.8	8.9	97/44.1	8.6	18.5	48/22.3	19.6	15.4	<0.001
	Lung	7/7.1	0.0	0.0	42/32.0	0.7	7.8	83/49.9	5.4	11.6	39/26.6	9.5	7.5	<0.001
	Other	91/59.1	2.8	73.7	235/143.4	6.3	70.0	262/133.0	21.0	45.1	118/52.6	49.7	39.1	<0.001
Hodgkin Lymphoma (women)	Total[4]	66/38.6	8	100	316/104.2	44.7	100	374/100.8	119.5	100	147/44.6	168.6	100	<0.001
	Breast	20/17.0	0.9	11.3	168/52.0	24.5	54.8	181/48.8	57.8	48.4	62/18.4	71.8	42.6	<0.001
	Lung	7/1.0	1.8	22.5	25/4.8	4.3	9.6	48/8.0	17.5	14.6	21/5.2	26	15.4	<0.001
	Other	39/20.6	5.4	67.5	123/47.4	16	35.8	145/44.0	44.2	37.0	64/21.0	70.8	42	<0.001
Hodgkin Lymphoma (men)	Total[5]	51/25.1	5.9	100	192/72.9	19.5	100	289/105.1	60.2	100	171/68.8	121.9	100	<0.001
	Lung	6/2.1	0.9	15.3	56/9.8	7.6	38.8	82/17.5	21.1	35.0	54/11.9	50.2	41.2	<0.001
	Other	45/23.0	5.0	84.7	136/63.1	11.9	61.3	207/87.7	39.1	65.0	117/56.9	71.7	58.8	<0.001
Thyroid (women)	Total[6]	61/47.0	5.0	100	155/107.8	13.6	100	133/95.1	23.9	100	48/38.9	21.9	100	0.048
	Breast	27/22.1	1.7	34.0	63/53.2	2.8	20.8	59/41.2	11.2	46.9	21/13.7	17.6	80.4	0.061
	Other	34/24.9	3.3	66.0	92/54.6	10.7	79.2	74/53.9	12.7	53.1	27/25.2	4.3	19.6	0.179

Abbreviations: FPN - First primary neoplasm, SPN- subsequent primary neoplasm, O – observed number of SPNs, E- Expected number of SPNs, AER- absolute excess risk, CI-confidence interval, %AER – percentage of total AER

* Negative numbers for the AER

† Where the estimated AER for a specific SPN was negative then this was ignored and the percentages were based on the positively value AERs – the excesses.

‡ From an externally controlled Poisson regression model which contained the following factors: attained age, decade of diagnosis and age at diagnosis.
[1]All SPNs after cancer in women excluding SPNs of the breast
[2]All SPNs after cancer in women excluding SPN of genital sites
[3]All SPNs after cancer in men excluding SPN of Other genital sites (prostate sites allowed)
[4]All solid SPNs after cancer in women (excluding non-solid tumours)
[5]All solid SPNs after cancer in men (excluding non-solid tumours)
[6]All SPNs after cancer in women excluding SPNs of the thyroid

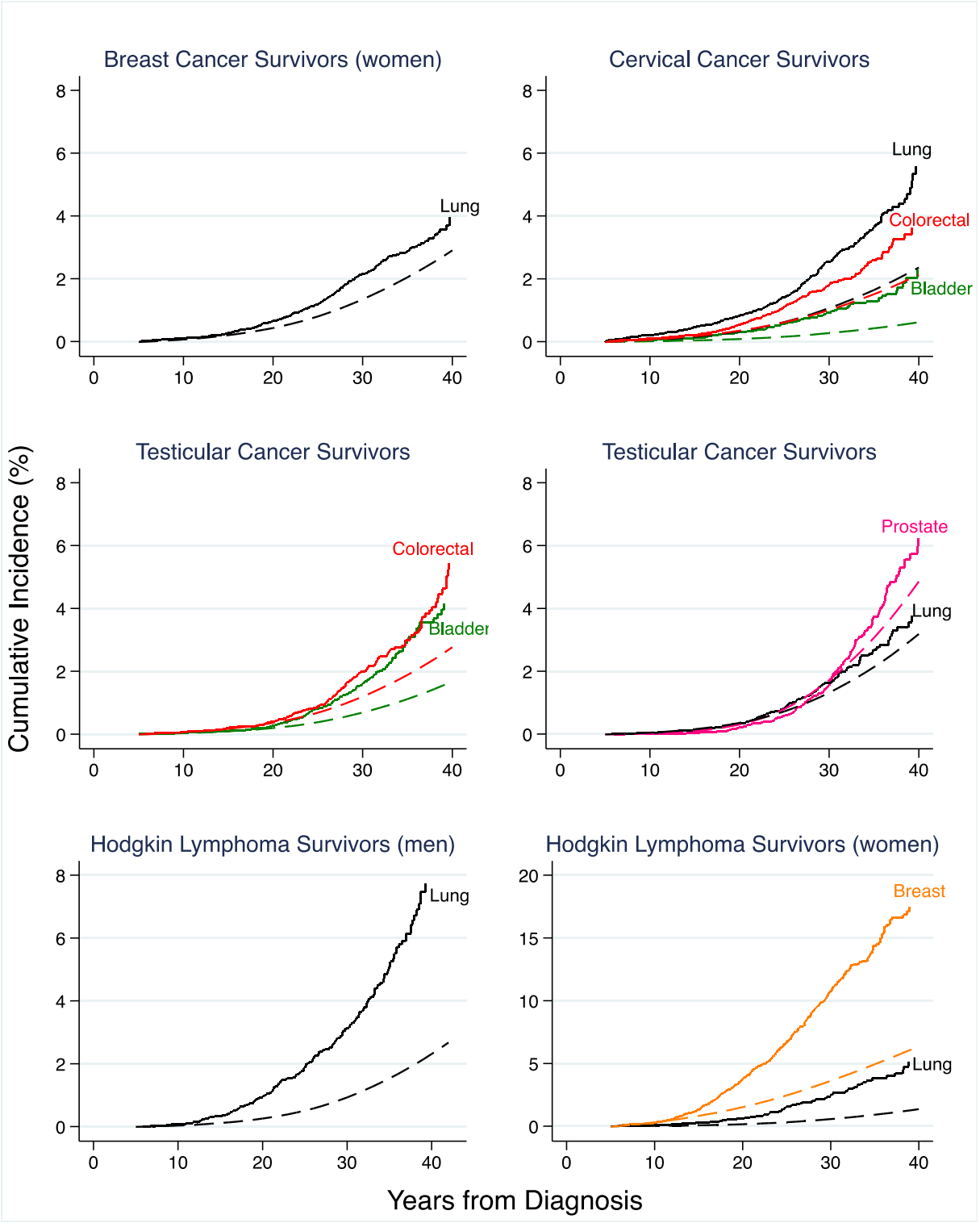


Figure 2.1: Observed (solid) and expected (dashed) cumulative incidence of specific SPNs among survivors of breast cancer, cervical cancer, testicular cancer, and Hodgkin lymphoma.
Note – different scale for Hodgkin lymphoma in women.

Chapter 3

Risk of cerebrovascular events in 178,962 5-year survivors of cancer diagnosed aged 15-39 years

3.1 ABSTRACT

Background: Survivors of teenage and young adult (TYA) cancer are at risk of cerebrovascular events, but the magnitude of and extent to which this risk varies by cancer type, decade of diagnosis, age at diagnosis and attained age remains uncertain. This is the largest ever cohort study to evaluate the risks of hospitalisation for a cerebrovascular event among long-term survivors of TYA cancer.

Methods: The population-based Teenage and Young Adult Cancer Survivor Study (N=178,962) was linked to Hospital Episode Statistics data for England to investigate the risks of hospitalisation for a cerebrovascular event among 5-year survivors of cancer diagnosed when aged 15-39 years. Observed numbers of first hospitalisations for cerebrovascular events were compared to that expected from the general population using standardised hospitalisation ratios (SHR) and absolute excess risks (AER) per 10,000 person-years. Cumulative incidence was calculated with death considered a competing risk.

Results: Overall, 2,782 cancer survivors were hospitalised for a cerebrovascular event—40% higher than expected (SHR=1.4, 95% confidence interval [CI]=1.3-1.4). Survivors of central nervous system (CNS) tumours (SHR=4.6, CI=4.3-5.0), head & neck tumours (SHR=2.6, CI=2.2-3.1) and leukaemia (SHR=2.5, CI=1.9-3.1) were at greatest risk. Men had a significantly higher AER than women (AER=7 versus 3), especially among head & neck tumour survivors (AER=30 versus 11). By age 60, 9%, 6% and 5% of CNS tumour, head & neck tumour, and leukaemia survivors, respectively, had been hospitalised for a cerebrovascular event. Beyond age 60, every year 0.4% of CNS tumour survivors were hospitalised for a cerebral infarction (versus 0.1% expected). Whereas at any age, every year 0.2% of head & neck tumour survivors were hospitalised for a cerebral infarction 7 (versus 0.06% expected).

Conclusions: Survivors of a CNS tumour, head & neck tumour, and leukaemia are particularly at risk of hospitalisation for a cerebrovascular event. The excess risk of cerebral infarction among CNS tumour survivors increases with attained age. For head & neck tumour survivors this excess risk remains high across all ages. These groups of survivors, and in particular men, should be considered for surveillance of cerebrovascular risk factors and potential pharmacological interventions for cerebral infarction prevention.

3.2 INTRODUCTION

Improvements in survival of cancer in teenagers and young adults (TYA, age 15-39 years) over the last few decades has resulted in current 5-year relative survival of over 80% [11]. This has resulted in a large population of cancer survivors, who may be at increased risk of treatment related long-term adverse health effects[3, 9]. Notwithstanding this, TYA cancer survivors are an understudied population and little is known about the risks of long-term adverse health outcomes in this group[1, 167].

Previous studies of cancer survivors have observed an increased risk of cerebrovascular events after irradiation of the head, neck and mediastinum[42, 68, 70, 72-74, 168]. In addition to treatment, local recurrence and brain metastases are also potential causes of cerebrovascular events in cancer populations [169]. Development of a cerebrovascular event after treatment for cancer is a serious, and potentially life-threatening adverse event[26], yet only one other large-scale population-based study has explored the risk of hospitalisation for a cerebrovascular event in individuals diagnosed with cancer, between the ages of 15 and 39 years (n=43,154 1-year survivors) [39]. In this Danish study, there was a 30% increased risk of hospitalisation for a cerebrovascular event for all survivors combined than in the general population, however,

the risk varied by type of cerebrovascular event and cancer type. The magnitude of the effect of attained age, age at cancer diagnosis and decade of cancer diagnosis on the risk of specific types of cerebrovascular events (e.g. cerebral infarction, cerebral haemorrhage) has not previously been investigated and has often been encompassed within studies of all types of cardiovascular events combined[8, 39, 42].

Within the UK, the risk of having a cerebrovascular event doubles every decade after the age of 55 [170]. Currently it is unknown what the risk of cerebrovascular events is in TYA cancer survivors and whether this effect doubles beyond the age of 55. If this holds true for survivors of TYA cancer this could lead to a large population of cancer survivors developing a cerebrovascular event in older age.

To our knowledge, this is the largest study to investigate the risk of hospitalisation for specific cerebrovascular events in survivors of all and specific types of cancer diagnosed in individuals aged 15-39 years. In addition, this is the first study to investigate whether the risk of hospitalisation for a cerebrovascular event varies with attained age, age at diagnosis and decade of diagnosis.

3.3 METHODS

3.3.1 Teenage and Young Adult Cancer Survivor Study

The Teenage and Young Adult Cancer Survivor Study (TYACSS) is a large population-based cohort consisting of 200,945 5-year survivors of cancer diagnosed aged 15-39 years between 1971 and 2006 in England and Wales. The cohort was ascertained from cancer registrations recorded by the Office for National Statistics and the Welsh Cancer Registry. Cancer

registrations were coded according to the relevant revisions of the International Classification of Diseases (ICD) (topography) and International Classification of Diseases for Oncology (ICDO) (morphology). We mapped all ICD-topography and ICDO-morphology codes into 15 main cancer types based on the classification of cancers for TYAs [6, 13]. We refined the classification slightly to allow for inclusion of finer groupings of carcinomas (see Table 3.1). Ethical approval was provided by the National Research Ethics Service (ref: 16/LO/0895) and permission to process information without individual consent by the National Information Governance Board (NIGB) for Health and Social Care (ref: 3-03(c)2010).

3.3.2 Ascertainment of cerebrovascular events from Hospital Episodes Statistics

The inpatient Hospital Episode Statistics (HES) database is a national electronic database of routinely collected data on individual hospital admissions to National Health Service (NHS) and private (if care was commissioned by the NHS) hospitals in England. For this study HES inpatient data were available from April 1997 to December 2012. Prior to linking the survivor cohort by NHS number, date of birth, postcode and sex to the inpatient HES database, we excluded all Welsh survivors (N= 11,099 patients) due to HES being restricted to England only. Individuals were also excluded if they had died or emigrated before the start of the follow-up period (1st April 1997) (N=10,128 patients) (see Figure 3.1 for flow-diagram of exclusions). It was not possible to determine the actual linkage rate of the survivor cohort to the inpatient HES database as not all survivors would have been admitted to hospital within the HES years 1997-2012. For the vast majority of survivors the key linkage identifiers—NHS number, date of birth, postcode and sex—were available and it is thus more likely that such survivors would not have been admitted to hospital rather than an actual failure to link

the survivor to the correct HES record(s). Of the 179,718 survivors eligible to be linked with HES, 84% (150,942) had at least one inpatient admission record in HES.

Each inpatient admission initiates a record in the HES database and contains information on the date of admission, methods of admission and discharge, patient demographics, and up to 20 diagnosis variables containing information on the primary condition, conditions diagnosed during hospital admission, and any pre-existing co-morbidities. All diagnosis variables are coded using the International Classification of Disease version 10 (ICD-10) and are coded at the time of hospital discharge by trained clinical coders or clinicians using all available clinical notes[171]. Cerebrovascular events (ICD-10: I60-I68) were identified from all 20 diagnosis variables recorded in HES and categorised into the following subgroups: *subarachnoid haemorrhage* (ICD-10: I60), *cerebral haemorrhage* (ICD-10: I61-I62), *cerebral infarction/occlusion/stenosis* (ICD-10: I63, I65-I66), and *'other cerebrovascular event'* (ICD-10: I64, I67-I68—stroke not specified as haemorrhage or infarction (ICD-10: I64), other cerebrovascular events (ICD-10: I67), cerebrovascular disorders in diseases elsewhere classified (ICD-10:I68). If an individual developed the same type of cerebrovascular event more than once, only the first event was retained for the analysis to ensure that any cerebrovascular event was not counted more than once due to potential duplicate recordings. Individuals who developed a cerebrovascular event within the first 5 years from cancer diagnosis were excluded as time at risk started at 5-year survival. Individuals with a first event recorded as sequelae of cerebrovascular disease (ICD-10: I69), but no prior recorded cerebrovascular event in HES were also excluded, as such survivors would most likely have had a prior cerebrovascular event before April 1997. After these

exclusions, a cohort of 178,962 5-year survivors remained (see Figure 3.1 for flow-diagram of exclusions).

3.3.3 Statistical analysis

Individuals were followed-up for cerebrovascular events from 5-year survival or 1st April 1997, whichever date was most recent. Follow-up ended at the first occurrence of death, emigration, hospitalisation for a cerebrovascular event or study end date (31st December 2012). Cerebrovascular related hospitalisation rates for the general population were derived from the entire (anonymised) HES dataset for England (N=13,476,762) by dividing the number of individuals with a hospitalisation by the mid-year general population estimates[172] for each age (1-year bands), sex and calendar-year (1-year bands). The accumulated person-years within each corresponding age, sex and calendar year stratum in the survivor cohort were multiplied by the general population rates to obtain the expected number of cerebrovascular hospitalisations.

Analyses were conducted to investigate the risk of a hospitalisation for all cerebrovascular events combined and for specific types of cerebrovascular events. The observed number of hospitalisations for a cerebrovascular event was divided by the number expected from the general population (referred to as a standardised hospitalisation ratio (SHR)[8]). The absolute excess risk (AER) is the additional number of hospitalisation for a cerebrovascular event compared to that expected based on general population hospitalisation rates; it is calculated as the observed minus the expected number of hospitalisation divided by the person-years at risk. The AER has been expressed per 10,000 person-years throughout the manuscript [153]. For each cerebrovascular event subtype, SHRs and AERs were stratified by the following factors:

cancer diagnosis, sex, age at cancer diagnosis (15-19/20-24/25-29/30-34/35-39 years), decade of cancer diagnosis (1971-1979/1980-1989/1990-1999/2000-2006) and attained age (20-44/45-49/50-54/55-59/≥60 years). To investigate the simultaneous effect of these variables on the risk of hospitalisation for a cerebrovascular event, multivariable Poisson regression was conducted to derive relative risks (RR) and excess hospitalisation ratios (EHR). RRs can be interpreted as the ratio of the SHRs adjusted for potential confounders. EHRs can be interpreted as the ratio of the AERs adjusted for potential confounders[154]. Negative binomial regression was preferred to Poisson when the data showed signs of over-dispersion (see Table 3.2 for dispersion parameters and regression methods used). A likelihood ratio test was used to test for linear trend of a factor by comparing the log-likelihood of a model including the factor variable of interest (e.g. attained age (20-44/45-49/50-54/55-59/≥60 years)), which was coded such that it had the median value of the variable at each level, with the log-likelihood of a model without the factor variable of interest. Cumulative incidence with attained age as the time scale was calculated treating death as a competing risk. A p-value of <0.05 (2-sided test) was taken as statistically significant. All statistical analyses were conducted in Stata statistical software (version 14.1, Stata Corp., College Station, TX).

From here on "hospitalisation for a cerebrovascular event" and "cerebral infarction/occlusion/stenosis" will be referred to as "cerebrovascular event" and "cerebral infarction", respectively.

3.4 RESULTS

3.4.1 Cohort characteristics

A total of 178,962 5-year survivors of TYA cancer were included in the analysis, contributing 1,837,996 person-years of follow-up. Characteristics of the cohort can be found in Table 3.3. The median follow-up was 11.3 years (range: 0-15.8 years) with 36% of individuals followed for at least 15 years. In total, 2,782 (1.6%) individuals were hospitalised for at least one cerebrovascular event. With respect to specific types of cerebrovascular events; 618 (0.35% (0.18% expected)) individuals were hospitalised for a cerebral haemorrhage, 1,296 (0.72% (0.48% expected)) for a cerebral infarction, 262 (0.15% (0.15% expected)) for a subarachnoid haemorrhage and 1,114 (0.62% (0.49% expected)) for 'other cerebrovascular events'.

3.4.2 Risk of any cerebrovascular event

Survivors experienced a 40% significantly increased risk of developing any cerebrovascular event than that expected from the general population (SHR=1.4, 95% confidence interval [CI]=1.3-1.4); corresponding to four excess events per 10,000 person-years (PY) (Table 3.4). Women experienced significantly fewer excess cerebrovascular events than men (AER=3 and AER=7, respectively; $P_{heterogeneity}<0.001$). In terms of age at cancer diagnosis, SHRs for a cerebrovascular event were highest among individuals diagnosed with a cancer aged 15-19 years (SHR=3.6, CI=3.0-4.2; AER=9) and there was a significant trend for the SHR to decrease with increasing age at diagnosis ($P_{trend}<0.001$). The SHR declined significantly with attained age ($P_{trend}<0.001$), although the p-value for trend for the RR just fell short of significance when evaluated in the multivariable model ($P_{trend}=0.086$) (Table 3.5). The AERs remained elevated at all ages, however; the multivariable analysis showed a significant increasing trend in the number of excess cerebrovascular events with increasing attained age—survivors older than 60 years had 2-fold the number of excess cerebrovascular events than survivors aged 20-44 years (EHR=2.4, CI=1.5-4.1;$P_{trend}<0.001$) (Table 3.5).

With regards to TYA cancer type, survivors at the highest risk of developing a cerebrovascular event were: central nervous system (CNS) tumour survivors (SHR=4.6, CI=4.3-5.0; AER=34); head & neck tumour survivors (SHR=2.6, CI=2.2-3.1; AER=22) and leukaemia survivors (SHR=2.5. CI=1.9-3.1; AER=10). The cumulative incidence of developing a cerebrovascular event by age 60 was 9.0%, 6.4% and 5.1% among CNS tumour, head & neck tumour and leukaemia survivors, respectively, whereas 2.3% was expected (Figure 3.2a). Due to having substantially increased risk, further analyses were conducted for CNS tumour, head & neck tumour and leukaemia survivors.

3.4.2.1 CNS tumour survivors

Survivors of all CNS tumour types were at increased risk of developing a cerebrovascular event, particularly, survivors of embryonal tumours (SHR=12.9, CI=8.0-19.7; AER=78) and glial tumours (SHR=10.8, CI=9.5-12.3; AER=72) (Table 3.6). The SHR was highest among survivors diagnosed when aged 15-19 years (SHR=12.7, CI=10.1-15.9); however survivors aged 35-39 years at diagnosis were still at 3.5-fold increased risk (SHR=3.5, CI=3.0-4.0). The SHR declined with increasing attained age, however remained elevated among all ages ($P_{trend}<0.001$). In contrast, the AER increased with attained age ($P_{trend}<0.001$) reaching 55 additional hospitalisations per 10,000 PY within individuals aged ≥60 years (Figure 3.3, Table 3.6).

3.4.2.2 Head & neck tumour survivors

Among head & neck tumour survivors, men had a significantly greater AER for a cerebrovascular event than women (P_{trend}=0.002), with an excess of 30 events compared to 11 per 10,000 PY, respectively (Table 3.7). The AER remained significantly increased for all ages; however the multivariable analysis showed that the AER did not increase significantly with attained age (P_{trend}=0.071) (Figure 3.4, Table 3.8).

3.4.2.3 Leukaemia survivors

Survivors of all types of leukaemia were at an increased risk of developing a cerebrovascular event and risk did not depend on type of leukaemia ($P_{heterogeneity}$=0.130) (Table 3.9). Leukaemia survivors diagnosed aged 15-19 years had the greatest SHR (SHR=5.1, CI=2.8-8.6) and the SHR decreased significantly with older age at diagnosis (P_{trend}=0.007). The AER increased significantly with attained age until age 55 years (P_{trend}=0.014) reaching 20 additional hospitalisations per 10,000 PY within individuals aged 50-54 years.

3.4.3 Risk of a cerebral haemorrhage

The SHR for a cerebral haemorrhage was twice that expected (SHR=2.0, CI=1.8-2.1). The risk of developing a cerebral haemorrhage among survivors diagnosed more recently (1990-2006), was increased nearly 4-fold relative to that expected from the general population (SHR=3.7, CI=2.9-4.7); whereas it was only 20% increased among survivors diagnosed earlier (1971-1979) (SHR= 1.2, CI=1.0-1.4) (Table 3.4). This increase in risk for the recent treatment decade was further confirmed by the multivariable analysis (P_{trend}=0.005) (Table 3.10). In terms of attained age, the SHR was highest for survivors younger than 45 years

(SHR=3.6, CI=3.1-4.2) and declined with increasing attained age, however remained significantly elevated for all ages (SHR at age 60+years = 1.2, CI=1.0-1.4) (Table 3.5).

With regards to TYA cancer type, the SHR was highest among survivors of a CNS tumour and leukaemia, with an 8-fold (SHR=8.3, CI=7.2-9.6) and 5-fold (SHR=5.2, CI=3.4-7.6) increased risk, respectively (Table 3.4). The cumulative incidence of developing a cerebral haemorrhage by age 60 was 3.4% and 2.0% among CNS tumour and leukaemia survivors, respectively, whereas 0.4% was expected (Figure 3.2b). Notably, survivors of melanoma were at increased risk of developing a cerebral haemorrhage (SHR=2.0 CI=1.5-2.6); but were not at significantly increased risk of any other cerebrovascular event.

3.4.3.1 CNS tumour survivors

The risk of developing a cerebral haemorrhage was significantly elevated among all CNS tumour survivors. Survivors of glial tumours were at greatest risk (SHR=26.2, CI=21.5-31.6) (Table 3.6). The SHR and AER of developing a cerebral haemorrhage among CNS survivors diagnosed more recently (1990-2006), was 27-fold increased relative to that expected from the general population (SHR=26.5, CI=18.6-36.7; AER=20); whereas it was only 4-fold increased among survivors diagnosed earlier (1971-1979) (SHR= 4.2 , CI=2.7-6.1; AER=10). This increase in the SHRs and AERs by more recent treatment decade was confirmed by the multivariable analysis (P_{trend}<0.001 and 0.005, respectively) (Table 3.11).

3.4.4 Risk of cerebral infarction

Overall, survivors had a 50% significantly increased risk of a cerebral infarction than that expected (SHR=1.5; CI=1.4-1.6; AER=2). In terms of age at cancer diagnosis, the SHR and

AER for a cerebral infarction was highest among survivors diagnosed aged 15-19 years (SHR=4.3, CI=3.3-5.4; AER=4) (Table 3.4); who had twice the risk of a cerebral infarction than survivors diagnosed aged 35-39 years (RR=0.5, CI=0.4-0.7) (Table 3.10). The AER increased with increasing attained age (P_{trend}<0.001) (Table 3.5); after adjusting for potential confounders, survivors aged over 60 years had 6-fold the number of excess cerebral infarction than survivors aged less than 45 years (EHR=5.6, CI=2.9-10.8).

With regards to TYA cancer type, the SHR was highest among survivors of CNS tumours (SHR=4.4, CI=3.9-5.0), head & neck tumours (SHR=3.5, CI=2.8-4.4), leukaemia (SHR=2.3, CI=1.5-3.3), and Hodgkin lymphoma (SHR=2.1, CI=1.8-2.5) (Table 3.4). The cumulative incidence of developing a cerebral infarction before age 60 was 4.2%, 3.6%, 2.3% and 2.0% among head & neck tumour, CNS tumour, leukaemia and Hodgkin lymphoma survivors, respectively, whereas 0.9% was expected (Figure 3.2c).

3.4.4.1 CNS tumour survivors

The risk of developing a cerebral infarction was significantly elevated among all CNS tumour survivors, with the exception of 'other specified' CNS tumour group. Survivors of embryonal tumours (SHR=18.8, CI=10.0-32.1) and germ cell tumours (SHR=10.5, CI=3.4-24.6) were at greatest risk (Table 3.6). The AER was substantially elevated among survivors of embryonal tumours, with 49 excess cerebral infarctions per 10,000 PY (Table 3.6). AERs increased sharply with attained age reaching 26 excess cerebral infarctions per 10,000 PY in survivors aged 60 years or older (P_{trend}<0.001) (Figure 2, Table 3.6). In terms of absolute risk, every year approximately 0.4% of CNS tumour survivors over age 60 years were hospitalised for a cerebral infarction compared to approximately 0.1% in the general population.

3.4.4.2 Head & neck tumour survivors

Among head & neck tumour survivors, the AER for a cerebral infarction was higher among men than women (AER=22 and AER=7, respectively; $P_{trend}<0.001$) (Table 3.7). The SHR decreased with attained age ($P_{trend}<0.001$), however remained elevated for all ages. The AER was high for all ages (AER=10-23); however did not vary significantly with attained age ($P_{trend}=0.159$) (Figure 3.4). In terms of absolute risk, every year approximately 0.2% of head & neck tumour survivors were hospitalised for a cerebral infarction compared to approximately 0.06% in the general population.

3.4.5 Risk of subarachnoid haemorrhage

The risk of being hospitalised for a subarachnoid haemorrhage among TYA cancer survivors did not differ significantly from that observed in the general population (SHR=1.0, CI=0.9-1.1; AER=0) (Results not shown).

3.4.6 Risk of 'other cerebrovascular events'

Survivors had a 40% significantly increased risk of any 'other cerebrovascular events' than that expected (SHR=1.4, CI=1.3-1.5; AER=2) (Table 3.4). The SHR and AER was highest among survivors diagnosed aged 15-19 years (SHR=4.1, CI=3.1-5.4; AER=3) (Table 3.4); survivors diagnosed aged 15-19 years had over twice the risk of developing 'other cerebrovascular events' than survivors aged 35-39 years at diagnosis (Table 3.10). The AER increased with increasing attained age reaching 2 per 10,000 person-years after age 60 years, which was confirmed by the multivariable analysis, where the EHR increased substantially with attained age ($P_{trend}<0.001$) (Table 3.5).

With regards to TYA cancer type, the risk was highest among survivors of: a CNS tumour (SHR=5.1, CI=4.5-5.8; AER=15), head & neck tumours (SHR=2.7, CI=2.0-3.5; AER=9) and leukaemia (SHR=2.6, CI=1.7-3.8; AER=4) (Table 3.4). The cumulative incidence of developing an 'other cerebrovascular event' by age 60 was 3.3%, 2.2% and 1.9% among CNS tumour, leukaemia and head & neck tumour survivors, respectively, whereas 0.8% was expected (Figure 3.2d).

3.4.6.1 CNS tumour survivors

Among CNS tumour survivors, the SHR and AER for 'other cerebrovascular events' was highest among survivors of embryonal tumours (SHR=20.2, CI=10.4-35.3 AER=46) and germ cell intracranial tumours (SHR=12.6, CI=4.1-29.5; AER=23) (Table 3.6). AERs increased substantially with attained age reaching 36 excess 'other cerebrovascular events' per 10,000 PY in CNS tumour survivors aged 60 years or older (P_{trend}<0.001) (Figure 3.3, Table 3.6).

3.4.6.2 Head & neck tumour survivors

Among head & neck tumour survivors, the AER increased significantly with attained age reaching 26 excess 'other cerebrovascular events' per 10,000PY in survivors aged 60 years or older (P_{trend}=0.002) (Figure 3.4, Table 3.7).

3.5 DISCUSSION

3.5.1 Main findings

In this largest ever study of TYA cancer survivors, we report a 40% increased risk of hospitalisation for a cerebrovascular event than that expected in the general population. TYA

cancer survivors are at 2-fold, 1.5-fold and 1.4-fold increased risk of a cerebral haemorrhage, cerebral infarction and `other cerebrovascular event`, respectively. By age 60, 9%, 6% and 5% of CNS tumour, head & neck tumour, and leukaemia survivors, respectively, had been hospitalised for a cerebrovascular event. Among TYA cancer survivors, men had a significantly higher number of excess cerebrovascular events than women, especially cerebral infarction among head and neck tumour survivors. We found that the excess risk of developing a cerebral infarction among CNS tumour survivors increases significantly with attained age. Beyond age 60, every year approximately 0.4% of CNS tumour survivors can expect to be hospitalised for a cerebral infarction. The excess risk of developing a cerebral infarction among head & neck tumour survivors did not vary with attained age but was consistently high. Every year approximately 0.2% of head & neck tumour survivors can expect to be hospitalised for a cerebral infarction.

3.5.2 Previous studies

The only other large-scale cohort investigating hospitalisation for cerebrovascular disease—a Danish cohort study of 43,153 1-year survivors of TYA cancer (age 15-39 years)—found a significant 1.3-fold increased risk of hospitalisation for any cerebrovascular disease for all survivors combined, which is comparable to the 1.4-fold increased risk observed in our study of 178,964 5-year survivors of TYA cancer [39]. In a smaller scale study; van Laar *et al*. did not observe a significantly increased risk of cerebrovascular disease among 1,880 5-year survivors of TYA cancer diagnosed between 15 and 29 years in Yorkshire, England; however the study included only 7 cerebrovascular events compared to 3,201 in the current study[8].

The Danish study by Rugbjerg *et al*. demonstrated that CNS tumour survivors had a substantially increased risk of being hospitalised for a cerebrovascular event (SHR=3.9, CI: 3.4-4.5), particularly for a cerebral haemorrhage (SHR=7.6, CI=5.7-10.2) and other undefined cerebrovascular disease (SHR=4.5, CI=3.6-5.5) [39]; these findings are generally consistent with the risk estimates observed in our study. In contrast, this study showed that CNS tumour survivors had a 4.4-fold (CI=3.9-5.0) increased risk of developing a cerebral infarction—significantly higher than the 2.9-fold (CI=2.2-3.8) risk observed by Rugbjerg *et al.* One explanation for this difference could be the more recent diagnosis period of our cohort (individuals diagnosed 1971-2006) compared to the Danish cohort (individuals diagnosed 1943-2009); hence the background risk of developing a cerebral infarction in our study was lower. To our knowledge, we provide for the first time, risk estimates for cerebrovascular disease by type of CNS tumour among TYA cancer survivors. Risk estimates for developing cerebrovascular disease for other tumour types, such as testicular, Hodgkin lymphoma, non-Hodgkin lymphoma, ovary, cervical, melanoma, thyroid and leukaemia were remarkably similar to those found by Rugbjerg *et al*[39].

3.5.3 Potential radiation-induced cerebrovascular disease

Although the mechanisms of radiation-induced cerebrovascular disease are unknown, cranial irradiation has been implicated in causing direct damage to endothelial cells of the cerebral arteries resulting in weakened vessels, accelerated atherosclerosis and vascular insufficiency secondary to stenosis or occlusion[68, 70, 173]. Previous studies among childhood CNS tumour survivors have reported a strong linear dose-response relationship between the amount of cranial irradiation exposure and risk of developing stroke[72-74, 168]. Prophylactic cranial irradiation for childhood leukaemia has also been shown to increase the risk of stroke in a

dose-dependent manner[72]. Given these observations among childhood cancer survivors, the substantially increased risks of cerebrovascular disease observed here among TYA survivors of CNS tumour and leukaemia are probably, to at least some extent, related to cranial irradiation as well. Nonetheless, some cerebrovascular events—particularly cerebral haemorrhage—may be caused by compression or damage of intracranial vessels from local recurrence of a CNS tumour or brain metastasis from other tumours (e.g. melanoma or head & neck cancer)[169]. This could explain the increase in cerebral haemorrhage among CNS tumour survivors treated most recently—a higher proportion of high-grade glial tumours (which are likely to recur) were observed in 1990-2006 than in previous decades (1971-1989). We cannot rule out the possibility that the increase in cerebral haemorrhage among CNS tumour survivors diagnosed more recently may be an artefact of greater frequency of CNS imaging or improved diagnosis of haemorrhage in more recent years. Melanoma survivors were at increased risk of a cerebral haemorrhage, but not any other type of cerebrovascular event. Melanoma metastases are commonly haemorrhagic [174] , therefore this increase could in fact be due to metastases to the brain from recurrent melanoma subsequent to 5-year survival.

This study observed a substantially increased risk of cerebral infarction among head and neck tumour survivors. Several previous studies—mainly among head and neck cancer patients diagnosed after age 40 years—have observed an increased risk of cerebral infarction after radiation to the head and neck [68-71]; this is more than likely due to radiation-induced damage of the carotid artery [173]. The exact mechanism underlying the radiation-induced damage of the carotid artery remains elusive; however it may be due to direct damage to endothelial cells which are very radiosensitive, injury to the microvasculature network or accelerated atherosclerosis [173, 175-178]. Radiation-induced carotid artery disease can lead to higher risk of

cerebral infarction due to stenosis of the carotid artery itself or by embolism of a dislodged thrombus blocking a cerebral artery [173]. However, there is the possibility that both head and neck cancer and cerebrovascular disease have a shared aetiology, thus smoking and alcohol may also be implicated in the increased risk of cerebrovascular disease. Nonetheless, all head and neck tumour survivors in the TYA cohort were diagnosed under age 40 years, and thus, exposure to smoking and alcohol is likely to play a lesser role in the aetiology of head and neck cancer compared to patients diagnosed after age 40 years[179]. In addition to carotid artery irradiation, an increased risk of cerebral infarction after mediastinal irradiation has also been observed among a population of Hodgkin lymphoma survivors, likely due to cardioemboli[42]. This, in addition to carotid artery irradiation could explain the 2-fold increased risk of cerebral infarction observed among Hodgkin lymphoma survivors in our study.

In this study, the risk of cerebral haemorrhage was greatest among CNS tumour survivors diagnosed most recently (2000-2006). The increasing trend observed within this diagnosis period was significant for glial tumour survivors only (results not shown). Among survivors, the proportion of gliomas considered high grade increased from 9.5% in 1971-1979 to 17.5% in 2000-2006. High grade tumours are more difficult to treat successfully and are likely to recur and it is thus not inconceivable that, although a greater proportion of these individuals are becoming 5-year survivors, more aggressive treatment and/or recurrence of the tumour could increase the risk of cerebral haemorrhage.

3.5.4 Recommendations for prevention of cerebrovascular disease

To our knowledge, there are no specific guidelines for stroke prevention among cancer survivors. The American Heart Association/American Stroke Association (AHA/ASA) and

Scottish Intercollegiate Guidelines Network (SIGN) guidelines recommend that individuals who are considered to be at high risk of stroke in the general population (e.g. history of coronary heart disease, previous stroke, high blood pressure, and diabetes mellitus) undergo regular blood pressure checks, implement lifestyle modifications (stop smoking and reduce alcohol consumption) and are considered for pharmacological intervention (e.g. antihypertensive medication and statins) to reduce the risk of stroke [180, 181]. In this study, the absolute excess risk of cerebral infarction among CNS tumour survivors and 'Other Cerebrovascular Event' among head & neck tumour survivors increased with attained age, resulting in substantial numbers of excess cerebral infarctions and 'Other Cerebrovascular Event' among older survivors. There is evidence suggesting that stroke risk is increased in cancer survivors treated with cranial irradiation in the absence of atherosclerotic risk factors [68, 74]. As previously mentioned, cranial irradiation has been implicated in causing accelerated atherosclerosis, therefore it could be argued that cranial irradiation itself is an atherosclerotic risk factor and patients treated with cranial irradiation should be considered at high risk such as patients with hypertension and diabetes. It may therefore not be unreasonable to suggest that TYA CNS tumour and head & neck tumour survivors (likely treated with head & neck irradiation) should be considered for pharmacological interventions even in the absence of other risk factors. A randomised intervention study may be required to ascertain if, and to the extent to which, these survivors would benefit from such treatments.

3.5.5 Study strengths and limitations

Most previous studies used questionnaires to ascertain cerebrovascular events which rely on self-report and may suffer from non-response or recall bias. A strength of the current study—in addition to the large cohort size—was that the ascertainment of cerebrovascular events was

entirely population-based through linkage of the TYACSS cohort with the population-based HES dataset, thereby eliminating potential non-response or recall bias. A limitation of our study is the lack of detailed treatment information, particularly the lack of detailed information on treatment with cranial radiotherapy (e.g. availability of cumulative radiation dose to the cranium). However, it would not be practically feasible to collect detailed information on treatment for the entire cohort of 178,962 survivors due the destruction of older medical notes in addition to cost and time restrictions. Nested case-control studies would be required to investigate the risks of developing cerebrovascular disease in relation to elements of treatment.

Modifiable lifestyle factors such as hypertension, diabetes, obesity and smoking may contribute to the elevated risk of cerebrovascular disease among cancer survivors treated with radiotherapy to the head, neck and mediastinum [42, 68, 69], however, we cannot confirm this as collecting information on lifestyle factors was beyond the scope of this study.

We acknowledge that survivors in this cohort were treated between 1971 and 2006, thus the findings presented may not be translatable to individuals treated with newer therapies in recent years e.g. proton beam therapy. Future prospective studies would be needed to investigate risks of cerebrovascular events after newer treatment protocols.

3.6 CONCLUSIONS

In this large scale study investigating cerebrovascular events in teenage and young adult cancer survivors, we found that survivors of a CNS tumour, head & neck tumour, and leukaemia are particularly at risk of hospitalisation for a cerebrovascular event. The excess

risk of developing a cerebral infarction among CNS tumour survivors increases with attained age. For head & neck tumour survivors this excess risk remains high across all ages. These groups of survivors, and in particular men, should be considered for surveillance of cerebrovascular risk factors and potential pharmacological interventions for cerebral infarction prevention.

Table 3.1: Groupings of TYA cancer based on the adolescent and young adult cancer classification scheme. (Refinements are highlighted in red)

Broader Groupings used in current study	AYA classification	AYA code
Leukaemia	Acute Lymphoid Leukaemia	1.1
	Acute Myeloid Leukaemia	1.2
	Chronic Myeloid Leukaemia	1.3
	Other and Unspecified Leukaemias	1.4
Non-Hodgkin Lymphoma	Non- Hodgkin Lymphoma, specified subtype	2.1.1
	Unspecified Non-Hodgkin Lymphoma	2.1.2
	Myeloma, mast cell tumours and miscellaneous lymphoreticular neoplasms NEC	9.2.3
Hodgkin Lymphoma	Hodgkin Lymphoma, specified subtype	2.2.1
	Hodgkin lymphoma NOS	2.2.2
Central Nervous System and Other Intracranial and Intraspinal Neoplasms	Pilocytic Astrocytoma	3.1.1
	Other specified low grade astrocytic tumours	3.1.2
	Glioblastoma and anaplastic astrocytoma	3.1.3
	Astrocytoma, NOS	3.1.4
	Oligodendroglioma	3.2.1
	Other specified glioma	3.2.2
	Glioma, NOS	3.2.3
	Ependymoma	3.3
	Medulloblastoma	3.4.1
	Supratentorial PNET	3.4.2
	Craniopharyngioma	3.5.1
	Other pituitary tumours	3.5.2
	Pineal tumours	3.5.3
	Choroid plexus tumours	3.5.4
	Meningioma	3.5.5
	Nerve sheath tumours of CNS	3.5.6
	Other specified intracranial and intraspinal neoplasms	3.5.7
	Unspecified malignant intracranial and intraspinal neoplasms	3.6.1
	Unspecified benign and borderline intracranial and intraspinal neoplasms	3.6.2
	Germ cell intracranial	6.2.1
Bone Neoplasms	Osteosarcoma	4.1
	Chondrosarcoma	4.2
	Ewing sarcoma of bone	4.3.1
	Ewing sarcoma of specified site other than bone	4.3.2
	Ewing sarcoma of unspecified site	4.3.3
	Other specified bone tumours	4.4.1

	Unspecified bone tumours	4.4.2
Soft Tissue Sarcoma	Fibrosarcoma	5.1.1
	Malignant Fibrous Histiocytoma	5.1.2
	Dermatofibrosarcoma	5.1.3
	Rhabdomyosarcoma	5.2
	Liposarcoma	5.3.1
	Leiomyosarcoma	5.3.2
	Synovial sarcoma	5.3.3
	Clear cell sarcoma	5.3.4
	Blood vessel tumours	5.3.5
	Nerve sheath tumours	5.3.6
	Alveolar soft part sarcoma	5.3.7
	Other specified	5.3.8
	Unspecified soft tissue sarcoma	5.4
Melanoma	Melanoma	7.1
Thyroid	Thyroid Carcinoma	8.1
Head and Neck	Nasopharyngeal carcinoma	8.2.1
	Other sites in lip, oral cavity and pharynx	8.2.2
	Nasal cavity, middle ear, sinuses, larynx and other and ill-defined head and neck	8.2.3
Lung	Trachea, bronchus and lung	8.3
Breast	Carcinoma of breast (women only)	8.4
Bladder	Carcinoma of bladder	8.5.2
	Unspecified malignant neoplasms, NEC (in bladder site)	10
	Unspecified benign and borderline neoplasms, NEC (in bladder site)	Not in AYA
	Benign and borderline neoplasms of bladder (ICDO3 code 8010-8589, 8982)	Not in AYA
GU Tract (other)	Carcinoma of kidney	8.5.1
	Carcinoma of other and ill-defined sites in GU tract	8.5.5
	Wilms tumour	9.1.1
Ovary	Carcinoma of ovary	8.5.3
	Germ cell and trophoblastic neoplasms of gonads (women only)	6.1
	Other specified gonadal tumours (women only)	9.2.2
Cervix	Carcinoma of cervix	8.5.4
Gastrointestinal Tract	Carcinoma of colon and rectum	8.6.1

	Carcinoma of stomach	8.6.2
	Carcinoma of liver and intrahepatic bile ducts	8.6.3
	Carcinoma of pancreas	8.6.4
	Carcinoma of other and ill-defined sites in GI tract	8.6.5
Testis	Germ cell gonadal (men only)	6.1
	Other specified gonadal tumours (men only)	9.2.2
Other	Other non-gonadal sites	6.2.2
	Non melanoma skin cancer (non-epithelial tumours only)	7.2
	Carcinoma of breast (men only)	8.4
	Adrenocortical carcinoma	8.7.1
	Carcinoma of other and ill-defined sites, NEC	8.7.2
	Neuroblastoma	9.1.2
	Other paediatric and embryonal, NEC	9.1.3
	Paraganglioma and glomus	9.2.1
	Other specified neoplasms, NEC	9.2.4
	Unspecified malignant neoplasms, NEC	10

Abbreviations: AYA= adolescents and young adults; NEC=not elsewhere classified; NOS= not otherwise specified; GI= gastrointestinal; GU=genitourinary; CNS= central nervous system; PNET= primitive neuroectodermal tumour.

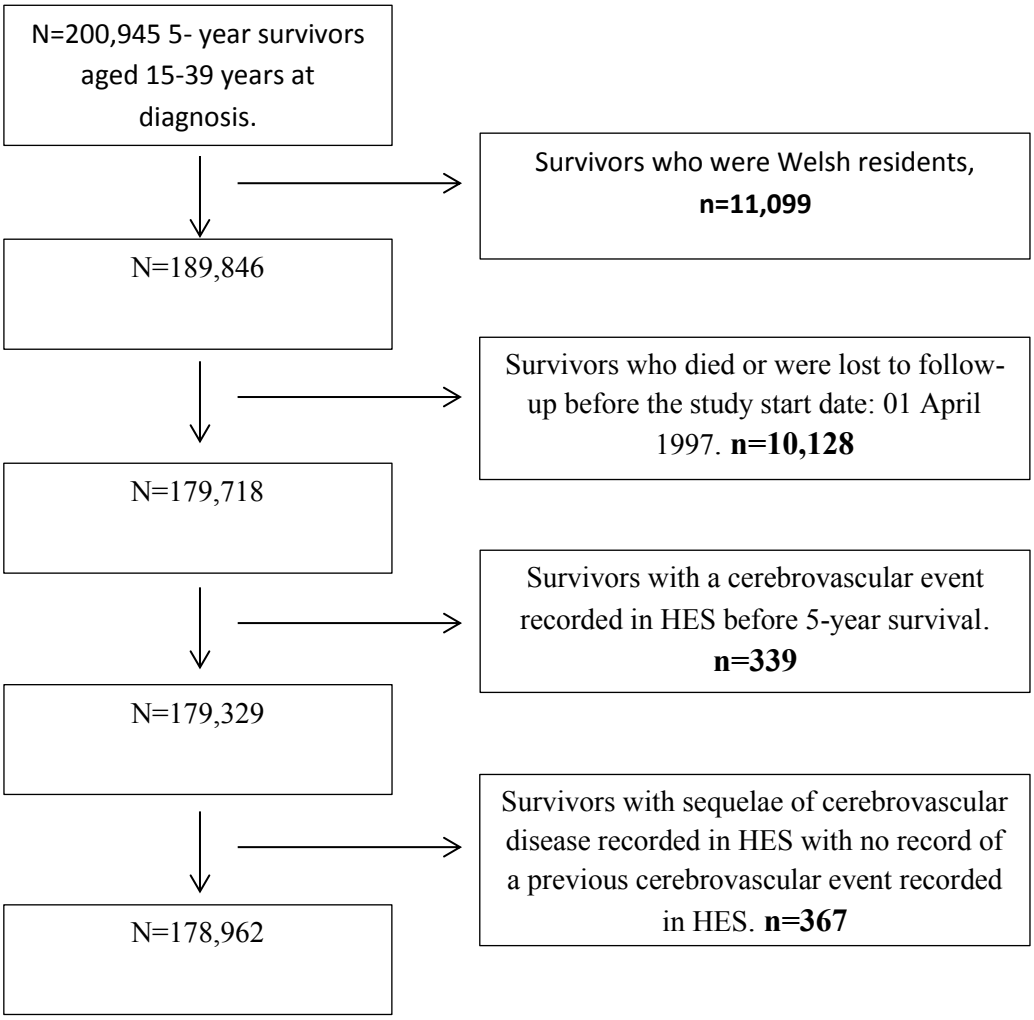


Figure 3.1: Flow diagram showing exclusions for the cohort of Teenage and Young Adult Cancer Survivor Study linked with HES.

Table 3.2: Test for over-dispersion - Dispersion parameters and associated p-values

	Dispersion parameter	p-value	Model for final analysis
Among all TYA cancer survivors			
Any cerebrovascular event	0.044	<0.001	Negative binomial
Cerebral haemorrhage	0.034	0.243	Poisson
Cerebral infarction	0.047	0.027	Negative binomial
'Other cerebrovascular events'	0	0.500	Poisson
CNS tumour survivors			
Any cerebrovascular event	0.104	0.014	Negative binomial
Cerebral haemorrhage	0	0.500	Poisson
Cerebral infarction	0	0.500	Poisson
'Other cerebrovascular events'	0.075	0.220	Poisson
Head & Neck tumour survivors			
Any cerebrovascular event	0	0.500	Poisson
Cerebral infarction	0	0.500	Poisson
'Other cerebrovascular events'	0	0.500	Poisson
Leukaemia survivors			
Any cerebrovascular event	0	0.500	Poisson

Abbreviations: TYA= teenage and young adult; CNS=central nervous system

Table 3.3: Cohort characteristics

		Number of 5-year survivors	Percentage
All Survivors	All Survivors	178,962	100%
FPN Diagnosis	Breast	30,956	17.3%
	Testicular	22,709	12.7%
	Cervix	21,220	11.9%
	Melanoma	20,709	11.6%
	CNS tumour	14,430	8.1%
	Glial Tumours[1]	3,985	(27.6%)
	Pituitary Tumour[2]	3,294	(22.8%)
	Meningioma	2,023	(14.0%)
	Embryonal Tumours[3]	273	(1.9%)
	Ependymoma	667	(4.6%)
	Craniopharyngioma	418	(2.9%)
	Germ Cell Intracranial	211	(1.5%)
	Other Specified[4]	2,654	(18.4%)
	Other Unspecified[5]	905	(6.3%)
	Hodgkin Lymphoma	15,120	8.5%
	NHL	8,402	4.7%
	Thyroid	7,343	4.1%
	Gastrointestinal	6,342	3.5%
	STS	5,570	3.1%
	Leukaemia	4,326	2.4%
	A L Leukaemia	1,076	(24.9%)
	C M Leukaemia	885	(20.5%)
	A M Leukaemia	1,570	(36.3%)
	Other Leukaemia	795	(18.4%)
	GU (other)	4,095	2.3%
	Ovary	4,419	2.5%
	Bladder	4,070	2.3%
	Head & Neck	3,573	2.0%
	Nasopharyngeal	438	(12.3%)
	lip/oral cavity/pharynx	2,543	(71.2%)
	Nasal cavity/middle ear	592	(16.6%)
	Other	5,678	3.2%
Sex	Men	68,845	38.5%
	Women	110,117	61.5%
Age at FPN Diagnosis	15-19	10,926	6.1%
	20-24	19,217	10.7%
	25-29	32,396	18.1%
	30-34	48,802	27.3%
	35-39	67,621	37.8%
Decade of FPN Diagnosis	1971-1979	19,048	10.6%
	1980-1989	43,313	24.2%
	1990-1999	62,854	35.1%
	2000-2006	53,747	30.0%
Attained Age	20-39	27,604	15.4%
	40-49	65,579	36.6%
	50-59	50,703	28.3%
	60+	35,076	19.6%

Abbreviations: FPN=first primary neoplasms; CNS=central nervous system; NHL=non-hodgkin lymphoma; STS=soft-tissue sarcoma; A L Leukaemia= acute lymphocytic leukaemia; C M Leukaemia= chronic myeloid leukaemia; A M Leukaemia= acute myeloid leukaemia; GU=genitourinary.

[1]For Glial Tumours, this category consists of pilocytic astrocytoma, other specified astrocytoma, glioblastoma, anaplastic astrocytoma, astrocytoma not otherwise specified, oligodendrogliomas, other specified glioma and glioma not otherwise specified.

[2]For Pituitary Tumour, this category consists of tumours of the pituitary (primarily pituitary adenomas), excluding craniopharyngioma

[3]For Embryonal Tumours, this category consists of medulloblastoma and supratentorial PNET

[4]For Other specified, this category consists of pineal tumours, choroid plexus tumours, CNS nerve sheath tumours and other specified CNS tumours

[5]For Other unspecified, this category consists of unspecified malignant CNS tumours and unspecified benign CNS tumour

Table 3.4: Standardised hospitalisation ratios and absolute excess risks of any cerebrovascular event, cerebral haemorrhage (ICD10: I61-I62), cerebral infarction (ICD10: I63, I65-66), other cerebrovascular event (ICD10:I64, I67-I68) by TYA cancer diagnosis, sex, age at diagnosis and decade of diagnosis.

	Any CV Event (ICD10: I60-I68)			**Cerebral Haemorrhage (ICD10: I61-I62)**			**Cerebral infarction (ICD10: I63, I65-I66)**			**Other CV Event (ICD10: I64, I67-I68)***		
	O	**SHR (95% CI)**	**AER (95% CI)**	**O**	**SHR (95% CI)**	**AER (95% CI)**	**O**	**SHR (95% CI)**	**AER (95% CI)**	**O**	**SHR (95% CI)**	**AER (95% CI)**
All Survivors	2782	1.4 (1.3,1.4)	4.2 (3.6,4.8)	618	2.0 (1.8,2.1)	1.6 (1.4,1.9)	1296	1.5 (1.4,1.6)	2.4 (2.0,2.7)	1114	1.4 (1.3,1.5)	1.7 (1.3,2.0)
FPN												
Breast	288	0.8 (0.7,0.9)	-2.0 (-3.1,-0.8)	48	1.0 (0.7,1.3)	-0.0 (-0.5,0.4)	127	0.9 (0.8,1.1)	-0.4 (-1.1,0.4)	117	0.8 (0.7,1.0)	-1.0 (-1.8,-0.3)
Testicular	278	1.0 (0.9,1.1)	0.1 (-1.3,1.4)	61	1.3 (1.0,1.7)	0.6 (-0.1,1.2)	128	1.0 (0.8,1.2)	-0.1 (-1.0,0.8)	97	0.9 (0.8,1.2)	-0.2 (-1.0,0.6)
Cervix	317	1.2 (1.1,1.4)	2.4 (0.9,3.8)	47	1.2 (0.9,1.6)	0.4 (-0.2,0.9)	137	1.4 (1.1,1.6)	1.5 (0.5,2.4)	149	1.4 (1.2,1.6)	1.7 (0.7,2.7)
Melanoma	155	0.8 (0.7,0.9)	-2.0 (-3.2,-0.8)	61	2.0 (1.5,2.6)	1.5 (0.7,2.3)	47	0.6 (0.4,0.8)	-1.7 (-2.4,-1.0)	47	0.6 (0.4,0.8)	-1.5 (-2.1,-0.8)
CNS tumour	616	4.6 (4.3,5.0)	33.9 (30.5,37.4)	183	8.3 (7.2,9.6)	11.2 (9.3,13.0)	256	4.4 (3.9,5.0)	13.8 (11.6,16.0)	268	5.1 (4.5,5.8)	15.1 (12.8,17.3)
Hodgkin Lymphoma	228	1.6 (1.4,1.8)	4.8 (3.1,6.6)	43	1.7 (1.3,2.4)	1.1 (0.3,1.9)	135	2.1 (1.8,2.5)	4.2 (2.9,5.6)	76	1.4 (1.1,1.7)	1.2 (0.2,2.2)
NHL	139	1.6 (1.4,1.9)	6.7 (3.8,9.5)	33	2.4 (1.6,3.3)	2.3 (1.0,3.7)	70	1.8 (1.4,2.3)	3.9 (1.9,6.0)	47	1.4 (1.0,1.9)	1.7 (0.1,3.4)
Thyroid	65	0.9 (0.7,1.2)	-0.6 (-2.7,1.5)	9	0.8 (0.4,1.6)	-0.2 (-1.0,0.6)	34	1.2 (0.8,1.7)	0.7 (-0.8,2.3)	27	1.0 (0.6,1.4)	-0.1 (-1.5,1.2)
Gastrointestinal	88	0.9 (0.7,1.2)	-1.0 (-3.9,1.9)	19	1.3 (0.8,2.1)	0.7 (-0.6,2.1)	43	1.0 (0.7,1.4)	0.1 (-2.0,2.1)	43	1.1 (0.8,1.5)	0.7 (-1.4,2.7)
STS	84	1.3 (1.0,1.6)	3.4 (0.4,6.5)	22	2.2 (1.4,3.3)	2.0 (0.5,3.6)	42	1.5 (1.1,2.0)	2.4 (0.2,4.5)	36	1.4 (1.0,2.0)	1.8 (-0.2,3.8)
Leukaemia	70	2.5 (1.9,3.1)	10.2 (6.2,14.2)	26	5.2 (3.4,7.6)	5.1 (2.7,7.6)	28	2.3 (1.5,3.3)	3.9 (1.3,6.4)	27	2.6 (1.7,3.8)	4.1 (1.6,6.6)
GU (other)	93	1.6 (1.3,1.9)	8.3 (3.7,12.8)	22	2.5 (1.6,3.8)	3.2 (1.0,5.4)	46	1.8 (1.3,2.4)	4.9 (1.7,8.1)	33	1.3 (0.9,1.9)	2.0 (-0.7,4.7)
Ovary	52	1.0 (0.7,1.3)	-0.3 (-3.1,2.5)	7	0.9 (0.4,1.9)	-0.1 (-1.2,0.9)	23	1.1 (0.7,1.6)	0.4 (-1.5,2.3)	20	0.9 (0.5,1.4)	-0.5 (-2.2,1.2)
Bladder	83	1.0 (0.8,1.2)	-0.3 (-4.1,3.5)	10	0.8 (0.4,1.4)	-0.6 (-1.9,0.7)	47	1.2 (0.9,1.6)	1.5 (-1.4,4.3)	32	0.9 (0.6,1.3)	-0.6 (-2.9,1.8)
Head & Neck	123	2.6 (2.2,3.1)	21.5 (15.4,27.7)	13	1.7 (0.9,3.0)	1.5 (-0.4,3.5)	75	3.5 (2.8,4.4)	15.0 (10.2,19.8)	51	2.7 (2.0,3.5)	8.9 (5.0,12.8)
Other	103	1.5 (1.2,1.9)	5.8 (2.6,9.1)	14	1.3 (0.7,2.2)	0.6 (-0.6,1.7)	58	2.0 (1.5,2.5)	4.7 (2.2,7.1)	44	1.6 (1.2,2.2)	2.8 (0.6,4.9)
$P_{heterogeneity}$		*<0.001*	*<0.001*		*<0.001*	*<0.001*		*<0.001*	*<0.001*		*<0.001*	*<0.001*
Sex												
Men	1322	1.5 (1.5,1.6)	6.6 (5.6,7.6)	322	2.2 (2.0,2.5)	2.5 (2.0,3.0)	659	1.6 (1.5,1.7)	3.5 (2.8,4.2)	505	1.6 (1.4,1.7)	2.5 (1.9,3.2)
Women	1460	1.3 (1.2,1.3)	2.7 (2.1,3.4)	296	1.8 (1.6,2.0)	1.1 (0.8,1.4)	637	1.4 (1.3,1.5)	1.6 (1.2,2.1)	609	1.3 (1.2,1.4)	1.1 (0.7,1.6)
$P_{heterogeneity}$		*<0.001*	*<0.001*		*0.004*	*<0.001*		*0.016*	*<0.001*		*0.001*	*0.006*
Age at FPN Diagnosis(years)												
15-19	148	3.6 (3.0,4.2)	8.9 (6.9,10.9)	44	5.3 (3.8,7.1)	3.0 (1.9,4.1)	67	4.3 (3.3,5.4)	4.3 (2.9,5.6)	56	4.1 (3.1,5.4)	3.5 (2.3,4.8)
20-24	219	2.0 (1.8,2.3)	5.2 (3.9,6.6)	53	2.7 (2.0,3.5)	1.6 (0.9,2.2)	101	2.3 (1.9,2.8)	2.7 (1.8,3.7)	81	2.2 (1.7,2.7)	2.1 (1.2,2.9)
25-29	407	1.6 (1.4,1.7)	4.2 (3.1,5.4)	91	2.1 (1.7,2.5)	1.3 (0.8,1.9)	192	1.8 (1.5,2.1)	2.4 (1.7,3.2)	164	1.7 (1.5,2.0)	2.0 (1.2,2.7)
30-34	722	1.3 (1.2,1.4)	3.6 (2.5,4.6)	176	2.1 (1.8,2.4)	1.8 (1.3,2.3)	318	1.4 (1.2,1.5)	1.7 (1.0,2.4)	255	1.2 (1.1,1.4)	0.8 (0.2,1.5)
35-39	1286	1.2 (1.2,1.3)	3.5 (2.4,4.6)	254	1.6 (1.4,1.8)	1.5 (1.0,2.0)	618	1.3 (1.2,1.4)	2.3 (1.6,3.1)	558	1.3 (1.2,1.4)	1.7 (1.0,2.4)
P_{trend}		*<0.001*	*<0.001*		*<0.001*	*0.079*		*<0.001*	*0.007*		*<0.001*	*0.002*
Decade of FPN Diagnosis												
1971-1979	809	1.1 (1.1,1.2)	3.9 (1.8,6.0)	118	1.2 (1.0,1.4)	0.8 (-0.0,1.6)	404	1.2 (1.1,1.4)	3.0 (1.5,4.5)	376	1.2 (1.1,1.3)	2.3 (0.8,3.7)
1980-1989	1097	1.5 (1.4,1.6)	5.6 (4.6,6.7)	235	2.0 (1.7,2.3)	1.9 (1.4,2.3)	519	1.6 (1.5,1.8)	3.2 (2.5,4.0)	448	1.5 (1.4,1.7)	2.5 (1.8,3.2)
1990-1999	700	1.6 (1.4,1.7)	3.4 (2.7,4.2)	195	2.5 (2.1,2.8)	1.6 (1.2,2.0)	309	1.8 (1.6,2.0)	1.8 (1.4,2.3)	239	1.5 (1.3,1.7)	1.1 (0.7,1.5)
2000-2006	176	1.7 (1.4,1.9)	3.1 (1.9,4.2)	70	3.7 (2.9,4.7)	2.2 (1.5,3.0)	64	1.5 (1.1,1.9)	0.9 (0.2,1.6)	51	1.4 (1.0,1.8)	0.6 (0.0,1.2)
P_{trend}		*<0.001*	*<0.001*		*<0.001*	*0.089*		*<0.001*	*<0.001*		*0.007*	*<0.001*

Abbreviations: CV=cerebrovascular; ICD= International classification of disease; O= observed; SHR=standardised hospitalisation ratio; AER=absolute excess risk; CI=confidence interval; FPN=first primary neoplasms; CNS=central nervous system; NHL=non-hodgkin lymphoma; STS=soft-tissue sarcoma; GU=genitourinary.

*Constituting ICD10: I64-Stroke not specified as haemorrhage or infarction (n=454); I67.0 – Dissection of cerebral arteries, non-ruptured (n=10); I67.1 – Cerebral aneurysm, non-ruptured (n=98); I67.2 – Cerebral atherosclerosis (n=38); I67.4-Hypertensive encephalopathy (n=12); I67.5-I67.8 – Other specified cerebrovascular disease (n=399); I67.9- Cerebrovascular disease, unspecified (n=244); I68 – Cerebrovascular disorders in diseases elsewhere classified (n=3).

Table 3.5: Standardised hospitalisation ratio, relative risk, absolute excess risk and excess hospitalisation ratio of any and specific cerebrovascular events according to attained age.

Cerebrovascular Event	Attained Age (years)	O	SHR (95% CI)	RR (95% CI)*	AER (95% CI)	EHR (95% CI)*
Any CV Event (ICD10: I60-I68)	20-44	549	2.0 (1.9,2.2)	1.0 Ref	3.7 (3.1,4.3)	1.0 Ref
	45-49	433	1.5 (1.3,1.6)	0.9 (0.7,1.0)	3.7 (2.6,4.7)	1.6 (1.2,2.2)
	50-54	512	1.5 (1.4,1.7)	0.9 (0.8,1.1)	6.1 (4.5,7.6)	2.1 (1.4,2.9)
	54-59	455	1.3 (1.2,1.4)	0.9 (0.7,1.0)	5.4 (3.3,7.4)	2.4 (1.5,3.6)
	60+	833	1.1 (1.0,1.2)	0.8 (0.7,1.0)	3.5 (0.9,6.2)	2.4 (1.5,4.1)
	P_{trend}		*<0.001*	*0.086*	*0.122*	*<0.001*
Cerebral Haemorrhage (ICD10: I61-I62)	20-44	193	3.6 (3.1,4.2)	1.0 Ref	1.8 (1.5,2.2)	1.0 Ref
	45-49	110	2.2 (1.8,2.6)	0.7 (0.6,0.9)	1.6 (1.0,2.1)	1.1 (0.7,1.6)
	50-54	106	1.9 (1.6,2.3)	0.7 (0.5,1.0)	1.7 (1.0,2.4)	1.2 (0.7,2.0)
	54-59	92	1.7 (1.4,2.1)	0.7 (0.5,1.0)	1.9 (1.0,2.8)	1.1 (0.6,2.2)
	60+	117	1.2 (1.0,1.4)	0.6 (0.4,0.8)	0.7 (-0.2,1.7)	1.0 (0.4,2.3)
	P_{trend}		*<0.001*	*0.016*	*0.137*	*0.610*
Cerebral infarction (ICD10: I63, I65-66)	20-44	197	2.2 (1.9,2.5)	1.0 Ref	1.4 (1.0,1.8)	1.0 Ref
	45-49	191	1.8 (1.5,2.0)	0.9 (0.7,1.1)	2.2 (1.5,2.9)	2.7 (1.8,4.1)
	50-54	242	1.8 (1.6,2.0)	0.9 (0.7,1.2)	3.7 (2.7,4.8)	3.7 (2.3,6.0)
	54-59	238	1.6 (1.4,1.8)	0.8 (0.6,1.1)	4.2 (2.7,5.7)	5.1 (2.9,8.8)
	60+	428	1.1 (1.0,1.3)	0.7 (0.5,0.9)	2.5 (0.6,4.4)	5.6 (2.9,10.8)
	P_{trend}		*<0.001*	*0.018*	*<0.001*	*<0.001*
Other CV event (ICD10: I64, I67-I68)	20-44	161	1.8 (1.6,2.1)	1.0 Ref	1.0 (0.6,1.3)	1.0 Ref
	45-49	160	1.6 (1.3,1.8)	1.0 (0.8,1.3)	1.5 (0.8,2.2)	3.0 (1.9,4.9)
	50-54	207	1.6 (1.4,1.9)	1.1 (0.9,1.4)	2.8 (1.8,3.8)	4.4 (2.6,7.4)
	54-59	184	1.3 (1.2,1.6)	1.0 (0.7,1.3)	2.3 (1.0,3.6)	4.6 (2.5,8.7)
	60+	402	1.1 (1.0,1.3)	0.9 (0.7,1.3)	2.3 (0.5,4.2)	6.4 (3.1,12.9)
	P_{trend}		*<0.001*	*0.605*	*<0.001*	*<0.001*

Abbreviations: CV=cerebrovascular; ICD= International classification of disease; O= observed; SHR=standardised hospitalisation ratio; AER=absolute excess risk; CI=confidence interval; RR=relative risk; EHR=excess hospitalisation ratio; ref= reference level

*Multivariable models and p-values are adjusted for cancer diagnosis, sex, age at cancer diagnosis, decade of cancer diagnosis and attained age

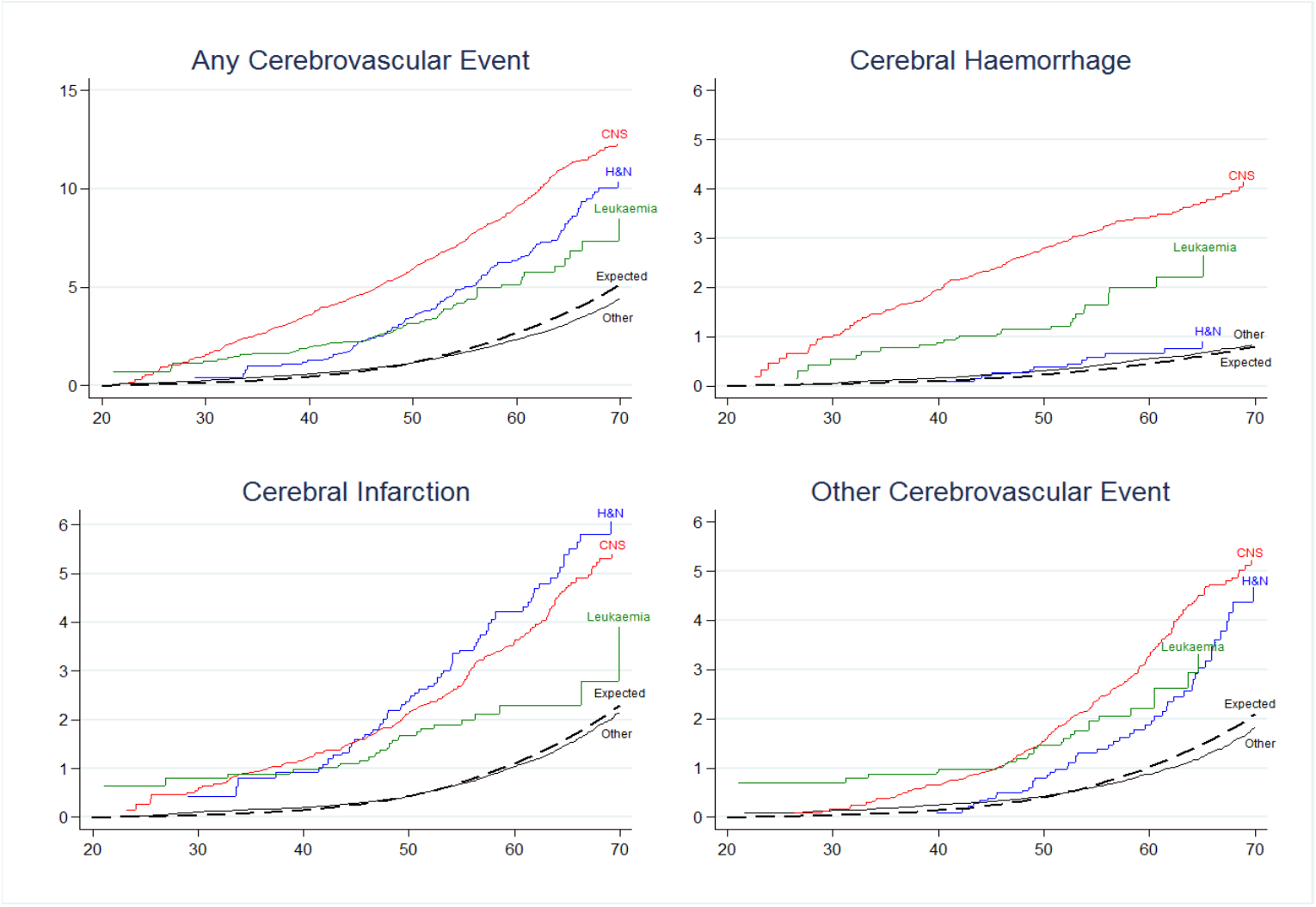


Figure 3.2: Cumulative incidence for all and specific types of cerebrovascular events, by attained age.
Abbreviations: H&N=head and neck, CNS= central nervous system. Other = all TYA cancers excluding CNS, H&N and leukaemia

Table 3.6: Standardised hospitalisation ratios and absolute excess risks of any cerebrovascular event, cerebral haemorrhage (ICD10: I61-I62), cerebral infarction (ICD10:I63, I65-66) or other cerebrovascular event (ICD10:I64, I67-I68) among CNS tumours survivors by tumour diagnosis, sex, age at diagnosis, decade of diagnosis and attained age

	Any CV Event (ICD10: I60-I68)			**Cerebral Haemorrhage (ICD10: I61-I62)**			**Cerebral infarction (ICD10: I63, I66-67)**			**Other CV Event (ICD10: I64, I67-I68)**		
	O	**SHR (95% CI)**	**AER (95% CI)**	**O**	**SHR (95% CI)**	**AER (95% CI)**	**O**	**SHR (95% CI)**	**AER (95% CI)**	**O**	**SHR (95% CI)**	**AER (95% CI)**
All CNS tumours	616	4.6 (4.3,5.0)	33.9 (30.5,37.4)	183	8.3 (7.2,9.6)	11.2 (9.3,13.0)	256	4.4 (3.9,5.0)	13.8 (11.6,16.0)	268	5.1 (4.5,5.8)	15.1 (12.8,17.3)
CNS tumour type												
Glial Tumour	254	10.8 (9.5,12.3)	72.3 (62.5,82.1)	108	26.2 (21.5,31.6)	32.1 (25.8,38.3)	94	9.3 (7.5,11.4)	25.9 (20.1,31.8)	89	10.1 (8.1,12.4)	24.8 (19.1,30.5)
Embryonal Tumour	21	12.9 (8.0,19.7)	78.0 (41.9,114.2)	*	*	*	13	18.8 (10.0,32.1)	49.1 (20.9,77.3)	12	20.2 (10.4,35.3)	45.6 (18.5,72.7)
Craniopharyngioma	24	6.0 (3.8,8.9)	43.9 (22.8,65.0)	5	7.3 (2.4,17.0)	9.3 (-0.2,18.7)	12	6.8 (3.5,11.9)	22.1 (7.5,36.8)	10	6.5 (3.1,12.0)	18.5 (5.0,32.0)
Other Pituitary Tumours	115	3.4 (2.8,4.0)	21.7 (16.1,27.4)	12	2.1 (1.1,3.7)	1.7 (-0.1,3.5)	55	3.8 (2.8,4.9)	10.8 (6.9,14.7)	61	4.6 (3.5,5.9)	12.8 (8.7,16.9)
Meningioma	52	2.1 (1.5,2.7)	12.9 (6.1,19.6)	13	3.4 (1.8,5.7)	4.3 (1.0,7.7)	24	2.2 (1.4,3.3)	6.2 (1.7,10.8)	20	1.9 (1.2,3.0)	4.6 (0.4,8.7)
Ependymoma	30	4.9 (3.3,7.0)	35.5 (19.5,51.5)	6	5.7 (2.1,12.4)	7.3 (0.2,14.3)	17	6.1 (3.6,9.8)	21.0 (9.1,32.9)	13	5.5 (3.0,9.5)	15.7 (5.3,26.2)
Germ Cell Intracranial	9	8.1 (3.7,15.3)	40.5 (10.3,70.8)	*	*	*	5	10.5 (3.4,24.6)	23.1 (0.7,45.5)	5	12.6 (4.1,29.5)	23.4 (1.1,45.7)
Other specified	56	2.0 (1.5,2.6)	10.3 (4.8,15.7)	22	4.8 (3.0,7.3)	6.5 (3.1,9.9)	19	1.5 (0.9,2.4)	2.4 (-0.8,5.6)	26	2.3 (1.5,3.4)	5.5 (1.8,9.2)
Other Unspecified	55	5.9 (4.4,7.7)	47.2 (32.2,62.2)	14	9.0 (4.9,15.0)	12.6 (5.2,20.1)	17	4.1 (2.4,6.5)	13.0 (4.8,21.2)	32	8.7 (5.9,12.2)	28.9 (17.6,40.3)
$P_{heterogeneity}$		*<0.001*	*<0.001*		*<0.001*	*<0.001*		*<0.001*	*<0.001*		*<0.001*	*<0.001*
Sex												
Men	339	4.8 (4.3,5.3)	40.8 (35.3,46.3)	105	8.5 (6.9,10.2)	13.9 (10.9,16.9)	140	4.2 (3.5,4.9)	16.0 (12.5,19.5)	153	5.8 (4.9,6.8)	19.1 (15.4,22.7)
Women	277	4.4 (3.9,4.9)	28.0 (23.8,32.3)	78	8.1 (6.4,10.2)	8.9 (6.6,11.1)	116	4.8 (3.9,5.7)	11.9 (9.2,14.7)	115	4.4 (3.7,5.3)	11.6 (8.9,14.3)
$P_{heterogeneity}$		*0.272*	*<0.001*		*0.805*	*0.006*		*0.280*	*0.066*		*0.028*	*0.001*
Age at FPN Diagnosis (years)												
15-19	79	12.7 (10.1,15.9)	37.7 (28.7,46.8)	28	21.8 (14.5,31.5)	13.7 (8.4,19.0)	32	13.6 (9.3,19.2)	15.2 (9.5,20.9)	30	14.8 (10.0,21.1)	14.4 (8.9,19.9)
20-24	67	6.3 (4.9,8.0)	25.5 (18.3,32.8)	17	8.5 (5.0,13.7)	6.7 (3.1,10.4)	28	6.7 (4.4,9.6)	10.7 (6.1,15.4)	28	7.5 (5.0,10.9)	10.9 (6.3,15.6)
25-29	113	5.7 (4.7,6.8)	33.1 (25.7,40.5)	34	9.7 (6.7,13.6)	10.7 (6.7,14.8)	48	5.8 (4.3,7.7)	14.0 (9.2,18.8)	49	6.7 (5.0,8.9)	14.7 (9.9,19.5)
30-34	146	4.1 (3.4,4.8)	32.5 (25.5,39.5)	53	9.1 (6.8,11.9)	13.8 (9.6,17.9)	52	3.3 (2.5,4.4)	10.7 (6.5,14.8)	56	4.0 (3.1,5.2)	12.3 (8.1,16.6)
35-39	211	3.5 (3.0,4.0)	38.7 (31.3,46.0)	51	5.4 (4.0,7.1)	10.5 (7.0,14.1)	96	3.5 (2.8,4.2)	17.4 (12.5,22.3)	105	4.1 (3.4,5.0)	20.3 (15.2,25.4)
P_{trend}		*<0.001*	*0.393*		*<0.001*	*0.791*		*<0.001*	*0.555*		*<0.001*	*0.111*
Decade of FPN Diagnosis												
1971-1979	142	3.3 (2.8,3.9)	53.4 (40.9,66.0)	26	4.2 (2.7,6.1)	10.4 (5.1,15.6)	59	3.0 (2.3,3.8)	20.6 (12.6,28.5)	83	4.5 (3.6,5.5)	34.2 (24.7,43.7)
1980-1989	234	4.6 (4.1,5.3)	38.5 (32.2,44.8)	49	5.8 (4.3,7.7)	8.4 (5.6,11.2)	107	4.9 (4.0,5.9)	17.7 (13.5,21.9)	115	5.9 (4.9,7.1)	19.8 (15.5,24.2)
1990-1999	179	5.4 (4.6,6.2)	24.8 (20.3,29.2)	72	11.9 (9.3,15.0)	11.1 (8.3,13.9)	71	5.4 (4.2,6.8)	9.8 (7.0,12.6)	57	4.9 (3.7,6.3)	7.7 (5.2,10.2)
2000-2006	61	8.5 (6.5,10.9)	31.5 (22.5,40.5)	36	26.5 (18.6,36.7)	20.3 (13.4,27.1)	19	6.3 (3.8,9.9)	9.3 (4.4,14.3)	13	5.4 (2.9,9.2)	6.2 (2.1,10.3)
P_{trend}		*<0.001*	*<0.001*		*<0.001*	*0.005*		*<0.001*	*<0.001*		*0.451*	*<0.001*
Attained Age (years)												
20-44	200	8.4 (7.3,9.7)	24.6 (20.7,28.5)	87	17.9 (14.4,22.1)	11.4 (8.9,14.0)	65	8.2 (6.3,10.4)	7.9 (5.7,10.1)	50	6.6 (4.9,8.7)	5.9 (4.0,7.8)
44-49	118	5.5 (4.6,6.6)	36.0 (28.1,43.9)	40	10.5 (7.5,14.4)	13.4 (8.8,17.9)	52	6.4 (4.8,8.5)	16.2 (11.0,21.5)	54	7.2 (5.4,9.5)	17.2 (11.9,22.5)
50-54	104	4.4 (3.6,5.4)	41.8 (31.4,52.1)	24	6.1 (3.9,9.1)	10.2 (5.3,15.1)	40	4.1 (2.9,5.5)	15.5 (9.1,21.8)	58	6.6 (5.0,8.5)	25.2 (17.6,32.9)
54-59	88	3.9 (3.1,4.8)	51.3 (36.8,65.7)	15	4.2 (2.4,7.0)	8.8 (3.0,14.6)	46	4.4 (3.2,5.9)	27.5 (17.2,37.8)	44	4.9 (3.6,6.6)	27.1 (17.1,37.2)
60+	106	2.5 (2.1,3.0)	54.6 (37.3,71.9)	17	2.9 (1.7,4.6)	9.1 (2.5,15.8)	53	2.4 (1.8,3.2)	26.0 (14.1,37.9)	62	3.2 (2.4,4.1)	35.7 (22.7,48.6)
P_{trend}		*<0.001*	*<0.001*		*<0.001*	*0.441*		*<0.001*	*<0.001*		*<0.001*	*<0.001*

Abbreviations: CV=cerebrovascular; ICD= International classification of disease; O= observed; SHR=standardised hospitalisation ratio; AER=absolute excess risk; CI=confidence interval; FPN=first primary neoplasms; CNS=central nervous system; NHL=non-Hodgkin lymphoma; STS=soft-tissue sarcoma; GU=genitourinary. *Omitted from table due to few events (less than 5 observed).

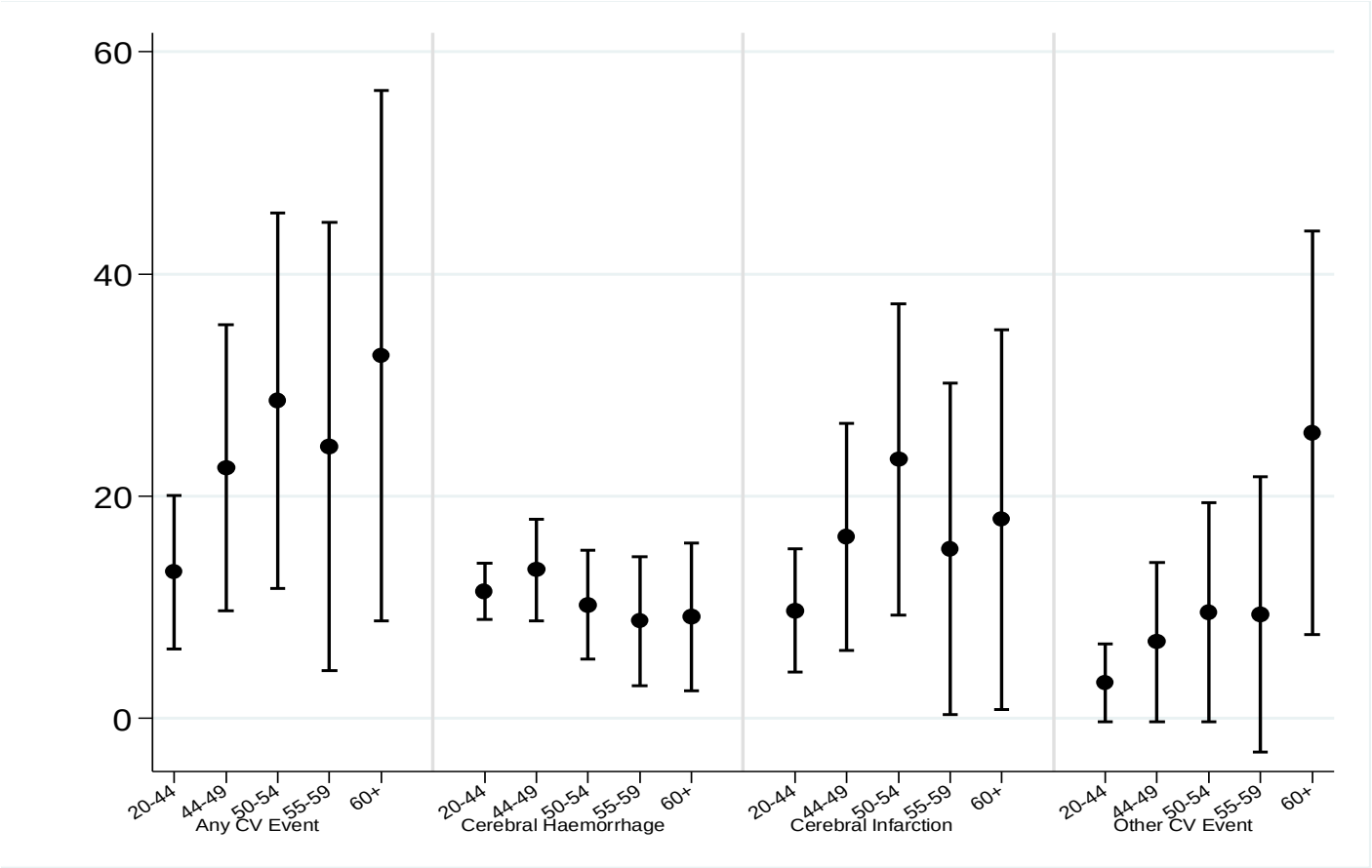


Figure 3.3: Absolute Excess Risk (95% CI) for any and specific types of cerebrovascular event (CV) according to attained age among survivors of CNS tumours.

Table 3.7: Standardised hospitalisation ratios and absolute excess risks of any cerebrovascular event, cerebral infarction (ICD10: I63, I65-66) or other cerebrovascular event (ICD10: I67-I68) among survivors of head and neck tumours by sex, age at diagnosis, decade of diagnosis and attained age

	Any CV Event (ICD10: I60-I68)			**Cerebral infarction (ICD10: I63, I65-66)**			**Other CV Event (ICD10: I64, I67-I68)**		
	O	**SHR (95%CI)**	**AER (95%CI)**	**O**	**SHR (95%CI)**	**AER (95%CI)**	**O**	**SHR (95%CI)**	**AER (95%CI)**
All HN tumours	123	2.6 (2.2,3.1)	21.5 (15.4,27.7)	75	3.5 (2.8,4.4)	15.0 (10.2,19.8)	51	2.7 (2.0,3.5)	8.9 (5.0,12.8)
Sex									
Men	91	2.9 (2.3,3.6)	30.4 (20.9,39.9)	58	3.8 (2.9,4.9)	21.5 (14.0,29.0)	36	2.9 (2.0,4.0)	11.7 (5.8,17.5)
Women	32	2.1 (1.4,2.9)	10.5 (3.5,17.6)	17	2.8 (1.6,4.4)	6.9 (1.8,12.0)	15	2.3 (1.3,3.8)	5.4 (0.6,10.2)
$P_{heterogeneity}$		*0.098*	*0.002*		*0.258*	*0.001*		*0.494*	*0.027*
Age at FPN Diagnosis (years)									
15-24	12	4.6 (2.4,8.0)	16.0 (4.4,27.6)	8	7.8 (3.3,15.3)	11.9 (2.4,21.3)	*	*	*
25-29	14	2.6 (1.4,4.3)	13.5 (1.9,25.2)	8	3.3 (1.4,6.5)	8.8 (0.1,17.5)	8	3.9 (1.7,7.6)	9.4 (0.6,18.1)
30-34	31	2.5 (1.7,3.6)	20.4 (8.6,32.3)	18	3.2 (1.9,5.1)	13.5 (4.5,22.4)	13	2.7 (1.4,4.5)	8.7 (1.1,16.3)
35-39	66	2.5 (1.9,3.2)	28.1 (16.8,39.4)	41	3.3 (2.4,4.5)	20.1 (11.3,28.9)	27	2.4 (1.6,3.5)	11.0 (3.9,18.1)
P_{trend}		*0.152*	*0.053*		*0.116*	*0.106*		*0.288*	*0.096*
Decade of FPN Diagnosis									
1971-1979	35	1.8 (1.3,2.5)	25.5 (6.8,44.2)	19	2.0 (1.2,3.2)	15.2 (1.7,28.8)	19	2.2 (1.3,3.4)	16.1 (2.7,29.6)
1980-1989	40	2.5 (1.8,3.4)	21.0 (10.1,31.9)	25	3.4 (2.2,5.1)	15.5 (6.9,24.0)	18	2.8 (1.7,4.5)	10.1 (2.9,17.3)
1990-2006	48	4.2 (3.1,5.6)	20.5 (12.9,28.1)	31	6.5 (4.4,9.2)	14.6 (8.5,20.7)	14	3.5 (1.9,5.9)	5.6 (1.5,9.7)
P_{trend}		*<0.001*	*0.799*		*<0.001*	*0.991*		*0.158*	*0.119*
Attained Age (years)									
20-44	23	4.6 (2.9,6.8)	13.2 (6.3,20.1)	15	8.6 (4.8,14.2)	9.7 (4.2,15.3)	6	3.7 (1.4,8.1)	3.2 (-0.3,6.7)
44-49	22	3.8 (2.4,5.7)	22.6 (9.7,35.4)	14	6.2 (3.4,10.4)	16.3 (6.1,26.5)	7	3.4 (1.4,7.1)	6.9 (-0.3,14.0)
50-54	23	3.2 (2.1,4.9)	28.6 (11.7,45.5)	16	5.4 (3.1,8.7)	23.3 (9.3,37.3)	8	3.0 (1.3,6.0)	9.5 (-0.3,19.4)
54-59	18	2.3 (1.3,3.6)	24.5 (4.3,44.7)	10	2.7 (1.3,5.0)	15.3 (0.4,30.2)	7	2.3 (0.9,4.7)	9.3 (-3.0,21.7)
60+	37	1.8 (1.3,2.5)	32.7 (8.8,56.5)	20	1.8 (1.1,2.9)	17.9 (0.8,35.0)	23	2.4 (1.5,3.6)	25.7 (7.5,43.9)
P_{trend}		*<0.001*	*0.029*		*<0.001*	*0.159*		*0.215*	*0.002*

Abbreviations: CV=cerebrovascular; ICD= International classification of disease; O= observed; SHR=standardised hospitalisation ratio; AER=absolute excess risk; CI=confidence interval; FPN=first primary neoplasms; CNS=central nervous system; NHL=non-Hodgkin lymphoma; STS=soft-tissue sarcoma; GU=genitourinary.
*Omitted from table due to few events (less than 5 observed).

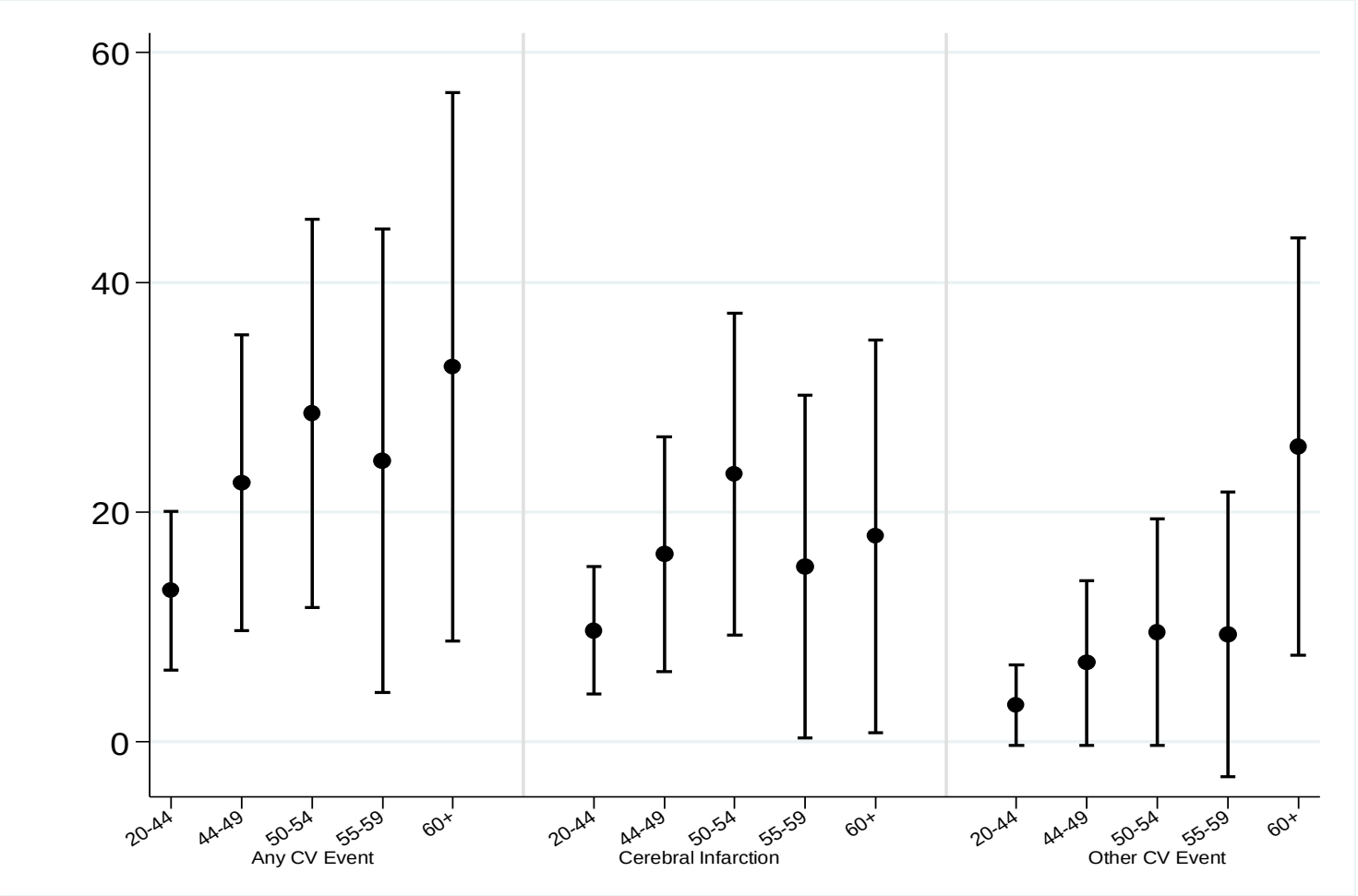


Figure 3.4: Absolute Excess Risk (95% CI) for any and specific types of cerebrovascular (CV) event according to attained age among survivors of head & neck tumours.

Table 3.8: Relative risks and excess hospitalisation ratios of any cerebrovascular event, cerebral infarction (ICD10: I63, I65-66) or 'other cerebrovascular event' (ICD10: I64, I67-I68) among survivors of head and neck tumours by sex, age at diagnosis and decade of diagnosis.

	Any CV Event		**Cerebral infarction**		**Other Cerebrovascular Event**	
	RR (95% CI)	**EHR (95% CI)**	**RR (95% CI)**	**EHR (95% CI)**	**RR (95%CI)**	**EHR (95%CI)**
Sex						
Men	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref
Women	0.7 (0.4,1.0)	0.3 (0.1,0.7)	0.7 (0.4,1.1)	0.3 (0.1,0.7)	0.8 (0.4,1.4)	0.5 (0.2,1.4)
$P_{heterogeneity}$	*0.035*	*0.001*	*0.110*	*0.005*	*0.377*	*0.238*
Age at FPN Diagnosis						
15-24	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref
25-29	0.6 (0.3,1.4)	0.5 (0.1,1.9)	0.6 (0.2,1.6)	0.5 (0.1,1.9)	1.1 (0.3,4.5)	1.4 (0.2,11.0)
30-34	0.6 (0.3,1.3)	0.8 (0.3,2.3)	0.7 (0.3,1.7)	0.8 (0.3,2.5)	0.7 (0.2,2.9)	1.0 (0.1,7.9)
35-39	0.6 (0.3,1.3)	0.8 (0.3,2.4)	0.8 (0.3,2.0)	0.9 (0.3,2.9)	0.6 (0.1,2.5)	0.7 (0.1,7.7)
P_{trend}	*0.378*	*0.995*	*0.867*	*0.785*	*0.242*	*0.612*
Decade of FPN Diagnosis						
1971-1979	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref
1980-1989	1.2 (0.7,2.1)	1.2 (0.4,3.6)	1.2 (0.6,2.4)	1.1 (0.3,3.7)	1.5 (0.7,3.1)	1.3 (0.4,5.0)
1990-2006	1.8 (0.9,3.7)	1.8 (0.5,6.7)	1.3 (0.5,3.3)	1.5 (0.4,5.8)	2.0 (0.6,6.3)	2.0 (0.3,13.7)
P_{trend}	*0.089*	*0.229*	*0.520*	*0.456*	*0.221*	*0.504*
Attained Age						
20-44	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref
44-49	0.9 (0.5,1.7)	1.7 (0.7,4.1)	0.7 (0.3,1.5)	1.5 (0.6,4.1)	1.1 (0.4,3.5)	3.0 (0.4,20.1)
50-54	0.9 (0.5,1.7)	2.6 (0.9,7.3)	0.6 (0.3,1.4)	2.5 (0.8,7.3)	1.1 (0.3,3.7)	5.0 (0.6,44.9)
54-59	0.7 (0.3,1.6)	2.2 (0.6,8.3)	0.3 (0.1,1.0)	1.7 (0.4,7.2)	0.9 (0.2,3.7)	5.9 (0.5,71.8)
60+	0.7 (0.3,1.6)	3.4 (0.7,15.3)	0.2 (0.1,0.8)	2.0 (0.4,10.7)	1.3 (0.3,5.5)	17.6 (1.2,250.6)
P_{trend}	*0.313*	*0.071*	*0.015*	*0.267*	*0.716*	*0.032*

Abbreviations: CV=cerebrovascular; ICD= International classification of disease; O/E= observed over expected; SHR=standardised hospitalisation ratio; AER=absolute excess risk; CI=confidence interval; RR=relative risk; EHR=excess hospitalisation ratio; ref= reference level; FPN=first primary neoplasms

*Multivariable models and p-values are adjusted for sex, age at cancer diagnosis, decade of cancer diagnosis and attained age

Table 3.9: Standardised hospitalisation ratios and absolute excess risks, relative risks and excess hospitalisation ratios of any cerebrovascular event among survivors of leukaemia by, type of leukaemia, sex, age at diagnosis, decade of diagnosis and attained age

	O	**SHR (95%CI)**	**RR (95%CI)***	**AER (95%CI)**	**EHR (95%CI)***
All Leukaemia	70	2.5 (1.9,3.1)		10.2 (6.2,14.2)	
Type of Leukaemia					
Acute Lymphoblastic	18	3.7 (2.2,5.9)	1.0 Ref	12.4 (4.6,20.3)	1.0 Ref
Acute Myeloid	16	1.7 (1.0,2.8)	0.6 (0.3,1.1)	4.5 (-0.8,9.7)	0.3 (0.1,1.7)
Chronic Myeloid	13	2.9 (1.6,5.0)	0.9 (0.4,2.0)	12.3 (2.1,22.5)	1.1 (0.3,3.8)
Other	23	2.3 (1.5,3.5)	0.9 (0.4,1.9)	15.9 (4.5,27.3)	1.0 (0.3,3.5)
$P_{heterogeneity}$		*0.13*	*0.297*	*0.15*	*0.322*
Sex					
Men	47	2.7 (2.0,3.6)	1.0 Ref	13.0 (7.1,18.9)	1.0 Ref
Women	23	2.1 (1.3,3.1)	0.8 (0.5,1.4)	6.6 (1.4,11.9)	0.5 (0.2,1.3)
$P_{heterogeneity}$		*0.29*	*0.409*	*0.262*	*0.258*
Age at FPN Diagnosis (years)					
15-19	14	5.1 (2.8,8.6)	1.0 Ref	12.0 (4.2,19.9)	1.0 Ref
20-24	6	2.2 (0.8,4.7)	0.4 (0.2,1.1)	4.7 (-2.3,11.8)	0.4 (0.1,1.8)
25-29	10	2.4 (1.2,4.4)	0.4 (0.2,1.0)	8.1 (-0.5,16.8)	0.4 (0.1,1.8)
30-34	22	3.0 (1.9,4.5)	0.5 (0.2,1.2)	17.4 (6.4,28.4)	0.6 (0.1,2.7)
35-39	18	1.6 (0.9,2.5)	0.2 (0.1,0.7)	7.3 (-2.0,16.6)	0.2 (0.0,1.3)
P_{trend}		*0.007*	*0.017*	*0.696*	*0.15*
Decade of FPN Diagnosis					
1971-1979	13	2.3 (1.2,3.9)	1.0 Ref	21.7 (0.5,42.9)	1.0 Ref
1980-1989	23	2.3 (1.4,3.4)	1.2 (0.5,2.9)	11.0 (3.0,19.0)	1.0 (0.2,4.5)
1990-2006	34	2.7 (1.9,3.7)	1.7 (0.6,4.7)	8.3 (3.9,12.8)	1.1 (0.2,5.9)
P_{trend}		*0.527*	*0.162*	*0.116*	*0.775*
Attained Age (years)					
20-44	22	2.7 (1.7,4.2)	1.0 Ref	5.5 (1.9,9.1)	1.0 Ref
44-49	19	3.1 (1.9,4.9)	1.6 (0.8,3.3)	17.5 (5.9,29.1)	5.0 (1.3,18.9)
50-54	14	2.6 (1.4,4.4)	1.6 (0.7,3.5)	20.4 (3.1,37.8)	6.0 (1.2,30.8)
55+	15	1.6 (0.9,2.7)	1.3 (0.5,3.6)	16.3 (-4.7,37.4)	7.9 (1.1,55.7)
P_{trend}		*0.142*	*0.429*	*0.014*	*0.01*

Abbreviations: O= observed; SHR=standardised hospitalisation ratio; AER=absolute excess risk; CI=confidence interval; RR=relative risk; EHR=excess hospitalisation ratio

* Multivariable models and p-values are adjusted for sex, age at cancer diagnosis, decade of cancer diagnosis and attained age

Table 3.10: Relative risks and excess hospitalisation ratios any cerebrovascular event*, cerebral haemorrhage (ICD10: I61-I62), cerebral infarction (ICD10: I63) or 'other cerebrovascular event' (ICD10: I65-I68) by TYA cancer diagnosis, sex, age at diagnosis and decade of diagnosis.

		Any CV Event		**Cerebral Haemorrhage**		**Cerebral infarction**		**Other Cerebrovascular Event**	
		RR (95% CI)	**EHR (95% CI)**	**RR (95% CI)**	**EHR (95% CI)**	**RR (95% CI)**	**EHR (95% CI)**	**RR (95% CI)**	**EHR (95% CI)**
FPN Diagnosis	Breast	0.6 (0.4,0.7)	0.0 (0.0,.)	0.5 (0.3,0.7)	0.1 (0.0,1.7)	0.5 (0.4,0.8)	0.1 (0.0,1.7)	0.7 (0.5,0.9)	0.0 (0.0,.)
	Testicular	0.6 (0.5,0.8)	0.1 (0.0,1.1)	0.5 (0.4,0.8)	0.1 (0.0,1.8)	0.5 (0.4,0.7)	0.0 (0.0,17.3)	0.6 (0.5,0.9)	0.0 (0.0,6127.0)
	Cervix	0.8 (0.6,1.0)	0.4 (0.2,1.2)	0.6 (0.4,0.9)	0.2 (0.0,1.3)	0.7 (0.5,1.0)	0.5 (0.2,1.4)	1.1 (0.8,1.6)	1.4 (0.4,5.1)
	Melanoma	0.5 (0.4,0.6)	0.0 (0.0,.)	0.8 (0.6,1.3)	0.8 (0.4,1.8)	0.3 (0.2,0.5)	0.0 (0.0,.)	0.5 (0.3,0.7)	0.0 (0.0,.)
	CNS tumour	2.9 (2.4,3.6)	6.9 (4.0,11.8)	3.5 (2.4,5.0)	5.8 (3.1,11.1)	2.4 (1.8,3.1)	4.9 (2.5,9.5)	3.6 (2.6,4.9)	12.2 (3.8,38.9)
	Hodgkin Lymphoma	0.9 (0.7,1.1)	0.7 (0.3,1.4)	0.7 (0.5,1.1)	0.3 (0.1,1.2)	1.0 (0.8,1.4)	1.3 (0.6,2.7)	0.9 (0.6,1.3)	0.5 (0.1,3.0)
	NHL	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref
	Thyroid	0.6 (0.4,0.8)	0.0 (0.0,.)	0.4 (0.2,0.8)	0.0 (0.0,.)	0.6 (0.4,1.0)	0.2 (0.0,3.9)	0.7 (0.4,1.2)	0.0 (0.0,.)
	Gastrointestinal	0.6 (0.5,0.8)	0.1 (0.0,37.2)	0.7 (0.4,1.1)	0.3 (0.0,1.9)	0.6 (0.4,0.9)	0.1 (0.0,345.9)	0.9 (0.6,1.3)	0.1 (0.0,2957.0)
	STS	0.8 (0.6,1.1)	0.9 (0.4,2.0)	1.0 (0.6,1.7)	0.9 (0.3,2.6)	0.8 (0.6,1.2)	0.9 (0.4,2.5)	1.0 (0.7,1.6)	1.8 (0.4,7.1)
	Leukaemia	1.3 (1.0,1.8)	2.1 (1.1,4.1)	1.9 (1.1,3.1)	2.4 (1.1,5.3)	1.1 (0.7,1.7)	1.7 (0.7,4.0)	1.6 (1.0,2.6)	4.0 (1.1,14.6)
	GU (other)	1.1 (0.8,1.4)	1.7 (0.8,3.5)	1.2 (0.7,2.1)	1.8 (0.8,4.4)	1.1 (0.7,1.6)	1.7 (0.7,4.0)	1.1 (0.7,1.7)	1.6 (0.3,8.0)
	Ovary	0.6 (0.5,0.9)	0.1 (0.0,3073.6)	0.4 (0.2,1.0)	0.0 (0.0,.)	0.6 (0.4,1.0)	0.1 (0.0,29.9)	0.7 (0.4,1.2)	0.2 (0.0,702.7)
	Bladder	0.7 (0.5,0.9)	0.2 (0.0,3.0)	0.4 (0.2,0.8)	0.1 (0.0,64.0)	0.7 (0.5,1.0)	0.3 (0.0,3.0)	0.7 (0.4,1.1)	0.0 (0.0,.)
	Head & Neck	1.7 (1.3,2.3)	3.8 (2.1,6.8)	0.8 (0.4,1.6)	0.8 (0.2,2.9)	2.1 (1.5,2.9)	4.6 (2.2,9.5)	2.0 (1.3,3.0)	5.6 (1.6,19.3)
	Other	0.9 (0.7,1.2)	1.0 (0.4,2.1)	0.6 (0.3,1.1)	0.5 (0.1,1.9)	1.1 (0.7,1.5)	1.3 (0.6,3.1)	1.2 (0.8,1.7)	1.9 (0.5,7.5)
	$P_{heterogeneity}$	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*
Sex	Men	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref
	Women	0.9 (0.9,1.1)	0.6 (0.5,0.8)	1.0 (0.8,1.2)	0.6 (0.5,0.8)	1.1 (0.9,1.2)	0.6 (0.5,0.8)	0.9 (0.8,1.0)	0.6 (0.5,0.8)
	$P_{heterogeneity}$	*0.316*	*<0.001*	*0.960*	*<0.001*	*0.551*	*<0.001*	*0.155*	*<0.001*
Age at FPN Diagnosis	15-19	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref
	20-24	0.7 (0.6,0.9)	0.7 (0.5,1.0)	0.7 (0.4,1.0)	0.6 (0.3,1.0)	0.7 (0.5,0.9)	0.7 (0.5,1.1)	0.6 (0.4,0.9)	0.6 (0.4,1.0)
	25-29	0.6 (0.5,0.7)	0.8 (0.6,1.1)	0.6 (0.4,0.9)	0.9 (0.6,1.5)	0.6 (0.4,0.8)	0.6 (0.4,1.0)	0.5 (0.4,0.7)	0.7 (0.4,1.1)
	30-34	0.6 (0.4,0.7)	0.8 (0.5,1.1)	0.7 (0.5,1.0)	1.1 (0.7,1.8)	0.5 (0.4,0.7)	0.5 (0.3,0.8)	0.4 (0.3,0.5)	0.4 (0.2,0.8)
	35-39	0.5 (0.4,0.7)	0.7 (0.5,1.1)	0.6 (0.4,0.9)	0.9 (0.5,1.6)	0.5 (0.4,0.7)	0.5 (0.3,0.8)	0.4 (0.3,0.6)	0.5 (0.3,0.9)
	P_{trend}	*<0.001*	*0.349*	*0.074*	*0.507*	*0.002*	*0.079*	*<0.001*	*0.124*
Decade of FPN Diagnosis	1971-1979	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref
	1980-1989	1.2 (1.1,1.4)	0.9 (0.7,1.2)	1.4 (1.1,1.8)	1.1 (0.6,1.9)	1.2 (1.0,1.4)	1.2 (0.8,1.8)	1.2 (1.0,1.4)	0.9 (0.6,1.3)
	1990-1999	1.2 (1.0,1.5)	0.8 (0.6,1.2)	1.4 (1.0,2.0)	1.3 (0.7,2.4)	1.2 (0.9,1.5)	1.3 (0.8,2.0)	1.2 (0.9,1.5)	0.7 (0.4,1.1)
	2000-2006	1.3 (1.0,1.6)	0.8 (0.5,1.3)	2.0 (1.3,3.0)	1.7 (0.8,3.5)	1.0 (0.7,1.4)	0.9 (0.4,1.8)	1.2 (0.8,1.7)	0.5 (0.2,1.2)
	P_{trend}	*0.013*	*0.239*	*0.005*	*0.070*	*0.479*	*0.831*	*0.161*	*0.026*

Abbreviations: CV=cerebrovascular; ICD= International classification of disease; O/E= observed over expected; SHR=standardised hospitalisation ratio; AER=absolute excess risk; CI=confidence interval; RR=relative risk; EHR=excess hospitalisation ratio; ref= reference level; FPN=first primary neoplasms; CNS=central nervous system; NHL=non-hodgkin lymphoma; STS=soft-tissue sarcoma; GU=genitourinary.
*Multivariable models and p-values are adjusted for cancer diagnosis, sex, age at cancer diagnosis, decade of cancer diagnosis and attained age

Table 3.11: Relative risks and excess hospitalisation ratios of any cerebrovascular event*, cerebral haemorrhage (ICD10: I61-I62), cerebral infarction (ICD10: I63, I65-66) or 'other cerebrovascular event '(ICD10: I64, I67-I68) among survivors of CNS tumours by CNS tumour diagnosis, sex, age at diagnosis and decade of diagnosis.

		Any CV Event (ICD10: I60-I68)		**Cerebral Haemorrhage (ICD10: I61-I62)**		**Cerebral infarction (ICD10: I63, I65-66)**		**Other Cerebrovascular Event (ICD10: I64, I67-I68)**	
		RR (95% CI)	**EHR (95% CI)**	**RR (95% CI)**	**EHR (95% CI)**	**RR (95% CI)**	**EHR (95% CI)**	**RR (95% CI)**	**EHR (95% CI)**
CNS tumour type	Glial Tumour	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref
	Embryonal Tumour	1.1 (0.7,1.8)	1.1 (0.7,1.9)	0.1 (0.0,0.9)	0.0 (0.0,.)	1.9 (1.0,3.4)	2.0 (1.1,3.7)	1.9 (1.0,3.4)	1.9 (1.0,3.7)
	Craniopharyngioma	0.6 (0.4,0.9)	0.5 (0.3,0.9)	0.3 (0.1,0.8)	0.3 (0.1,0.9)	0.8 (0.4,1.4)	0.7 (0.4,1.5)	0.7 (0.3,1.3)	0.6 (0.3,1.3)
	Other Pituitary Tumours	0.3 (0.3,0.4)	0.3 (0.2,0.4)	0.1 (0.1,0.2)	0.0 (0.0,0.1)	0.4 (0.3,0.6)	0.3 (0.2,0.5)	0.5 (0.4,0.7)	0.4 (0.3,0.6)
	Meningioma	0.2 (0.2,0.3)	0.1 (0.1,0.3)	0.2 (0.1,0.3)	0.1 (0.0,0.3)	0.3 (0.2,0.4)	0.2 (0.1,0.4)	0.2 (0.1,0.4)	0.1 (0.1,0.3)
	Ependymoma	0.5 (0.3,0.7)	0.4 (0.3,0.7)	0.2 (0.1,0.6)	0.2 (0.1,0.6)	0.7 (0.4,1.2)	0.7 (0.4,1.3)	0.6 (0.3,1.0)	0.5 (0.3,1.1)
	Germ Cell Intracranial	0.7 (0.3,1.3)	0.6 (0.3,1.3)	0.3 (0.1,1.3)	0.3 (0.1,1.4)	1.1 (0.4,2.6)	1.0 (0.4,2.6)	1.2 (0.5,3.0)	1.1 (0.4,3.0)
	Other specified	0.2 (0.2,0.3)	0.1 (0.1,0.2)	0.2 (0.1,0.3)	0.2 (0.1,0.3)	0.2 (0.1,0.3)	0.1 (0.0,0.3)	0.3 (0.2,0.4)	0.2 (0.1,0.4)
	Other Unspecified	0.6 (0.4,0.8)	0.6 (0.4,0.8)	0.4 (0.2,0.7)	0.4 (0.2,0.7)	0.5 (0.3,0.8)	0.4 (0.2,0.8)	0.9 (0.6,1.4)	1.0 (0.6,1.5)
	$P_{heterogeneity}$	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*
Sex	Men	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref
	Women	1.0 (0.9,1.2)	0.8 (0.6,1.0)	1.3 (0.9,1.7)	0.8 (0.6,1.2)	1.3 (1.0,1.7)	0.9 (0.6,1.2)	0.9 (0.7,1.1)	0.7 (0.5,0.9)
	$P_{heterogeneity}$	*0.627*	*0.059*	*0.133*	*0.325*	*0.034*	*0.390*	*0.307*	*0.003*
Age at FPN Diagnosis	15-19	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref
	20-24	0.6 (0.4,0.9)	0.8 (0.5,1.2)	0.5 (0.3,1.0)	0.6 (0.3,1.2)	0.6 (0.4,1.0)	0.7 (0.4,1.2)	0.6 (0.4,1.0)	0.7 (0.4,1.3)
	25-29	0.6 (0.5,0.9)	0.9 (0.6,1.3)	0.7 (0.4,1.1)	0.9 (0.5,1.7)	0.6 (0.4,1.0)	0.7 (0.4,1.2)	0.6 (0.4,1.0)	0.8 (0.5,1.4)
	30-34	0.5 (0.4,0.8)	1.0 (0.6,1.4)	0.7 (0.4,1.2)	1.3 (0.8,2.3)	0.4 (0.2,0.7)	0.5 (0.3,1.0)	0.5 (0.3,0.8)	0.7 (0.4,1.3)
	35-39	0.6 (0.4,0.8)	1.0 (0.7,1.6)	0.5 (0.3,0.9)	1.0 (0.5,1.9)	0.5 (0.3,0.9)	0.7 (0.3,1.3)	0.6 (0.3,1.0)	1.0 (0.5,1.9)
	P_{trend}	*0.007*	*0.600*	*0.083*	*0.371*	*0.022*	*0.335*	*0.116*	*0.631*
Decade of FPN Diagnosis	1971-1979	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref
	1980-1989	1.2 (0.9,1.5)	0.9 (0.7,1.3)	1.3 (0.7,2.1)	1.0 (0.5,2.1)	1.5 (1.0,2.1)	1.4 (0.9,2.3)	1.1 (0.8,1.5)	0.8 (0.6,1.3)
	1990-1999	1.2 (0.8,1.7)	0.7 (0.5,1.2)	2.0 (1.1,3.8)	1.4 (0.6,3.1)	1.4 (0.8,2.3)	1.2 (0.7,2.3)	0.8 (0.5,1.3)	0.5 (0.2,0.8)
	2000-2006	1.6 (1.1,2.6)	1.0 (0.6,1.7)	3.8 (1.8,8.0)	2.5 (1.0,5.9)	1.5 (0.7,3.0)	1.6 (0.7,3.5)	0.9 (0.4,1.8)	0.5 (0.2,1.2)
	P_{trend}	*0.067*	*0.712*	*<0.001*	*0.005*	*0.176*	*0.421*	*0.534*	*0.015*
Attained Age	20-44	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref	1.0 Ref
	44-49	0.9 (0.6,1.1)	1.7 (1.2,2.4)	0.9 (0.6,1.4)	1.7 (1.1,2.7)	1.0 (0.7,1.5)	2.9 (1.7,4.8)	1.3 (0.8,1.9)	3.1 (1.9,5.2)
	50-54	0.8 (0.6,1.1)	2.2 (1.5,3.2)	0.7 (0.4,1.3)	1.7 (0.9,3.1)	0.7 (0.5,1.2)	3.1 (1.7,5.7)	1.2 (0.7,1.8)	4.3 (2.4,7.6)
	54-59	0.8 (0.5,1.1)	2.4 (1.5,3.9)	0.6 (0.3,1.3)	1.1 (0.4,3.0)	0.9 (0.5,1.5)	6.1 (3.1,11.9)	0.9 (0.5,1.5)	4.2 (2.1,8.4)
	60+	0.6 (0.4,0.9)	2.8 (1.6,4.9)	0.5 (0.2,1.2)	1.5 (0.5,4.3)	0.6 (0.3,1.2)	7.0 (3.1,15.5)	0.6 (0.3,1.1)	5.3 (2.4,11.7)
	P_{trend}	*0.033*	*<0.001*	*0.144*	*0.131*	*0.203*	*<0.001*	*0.125*	*<0.001*

Abbreviations: CV=cerebrovascular; ICD= International classification of disease; O/E= observed over expected; SHR=standardised hospitalisation ratio; AER=absolute excess risk; CI=confidence interval; RR=relative risk; EHR=excess hospitalisation ratio; ref= reference level; FPN=first primary neoplasms

*Multivariable models and p-values are adjusted for CNS tumour type, sex, age at cancer diagnosis, decade of cancer diagnosis and attained age

Chapter 4

Cause-specific mortality in 17,280 5-year survivors of teenage and young adult central nervous system tumours

4.1 ABSTRACT

Background: Survival from central nervous system (CNS) tumours diagnosed in teenagers and young adults (TYA) has improved over recent years. This population of long-term cancer survivors are at increased risk of premature mortality. However, few studies have comprehensively investigated the risk of cause-specific mortality among long-term TYA CNS tumour survivors

Methods: The Teenage and Young Adult Cancer Survivor Study is a large population-based cohort of 200,945 5-year survivors of cancer diagnosed aged 15-39 years between 1971-2006 in England & Wales. The risk of cause-specific mortality was investigated using standardised mortality ratios (SMRs) and absolute excess risks (AERs) stratified by CNS tumour subtype, diagnosis era and years from diagnosis for the 17,280 5-year survivors diagnosed with a CNS tumour.

Results: Overall 4,099 deaths were observed which was 7-fold expected, and corresponded to 150 excess deaths per 10,000 person-years (SMR=6.6, 95% confidence interval [CI] =6.4-6.8; AER=150.4; CI=145.0-155.8). Neoplasms were the leading cause of death in early follow-up within survivors of all CNS tumour types. Beyond 25 years from diagnosis the majority of excess deaths were attributable to non-neoplastic causes for survivors of gliomas, craniopharyngioma, other pituitary tumours and ependymoma. Among glial tumour survivors, the AER for non-neoplastic mortality was 73 subsequent to 25 years from diagnosis, contributing 59% of the total AER—strokes contributed 30% of the total AER. Among pituitary tumour survivors, the AER for non-neoplastic deaths was 59 subsequent to 25 years from diagnosis, contributing 89% of the total AER—strokes and cardiac disease contributed 25% and 21% of the total AER, respectively. Reassuringly, the AER due to strokes significantly decreased in the most recent diagnosis era of survivors of glial and pituitary

tumours (Glial tumour: AER=19 in 1971-1979, AER=3 in 1990-2006; Pituitary tumour: AER=14 in 1971-1979; AER<1 in 1990-2006).

Conclusion: This largest ever study of TYA cancer survivors has identified an excess mortality due to both neoplastic and non-neoplastic causes within survivors of CNS tumours. Of major concern is the increased mortality due to strokes in long-term survivors of glial and pituitary tumours; in addition to the increased mortality due to cardiac diseases in long-term survivors of pituitary tumours. These non-neoplastic deaths are more likely preventable than neoplastic deaths with appropriate clinical follow-up and focus should be on preventing these deaths.

4.2 INTRODUCTION

Survival after central nervous system (CNS) tumours diagnosed in teenagers and young adults (TYA) has improved over recent years[11]— currently, individuals diagnosed with a CNS tumour (excluding pilocytic astrocytoma) aged 15-39 years have a 5-year relative survival of 57%[11]. This population of cancer survivors are potentially at increased risk of premature mortality. However, few studies have comprehensively investigated the risk of cause-specific mortality among long-term TYA CNS tumour survivors[23-26]. The paucity of published research has prevented the development of evidence-based clinical guidelines for the long-term follow-up of TYA CNS tumour survivors[1-3].

An increased risk of premature mortality relating to both neoplastic and non-neoplastic causes has been well established in survivors of childhood CNS tumours[92, 93, 128, 135, 182-184]. However, very little comparable information is available relating to survivors of TYA CNS tumours. A few studies have found an increased risk of premature mortality in TYA CNS tumour

survivors[23-26], but these were based on small cohorts, few non-neoplastic deaths and did not include survivors relating to the entire age range of TYA CNS tumours—aged 15 to 39 years at diagnosis. Only one study has investigated both neoplastic and non-neoplastic mortality within survivors of TYA CNS tumours diagnosed across a reasonably wide age range (1,135 5-year survivors, aged 20-34 years at diagnosis)[23]. The current study includes 15-fold the number of 5-year survivors and 8-fold the number of deaths than included in this previous study [23]. To our knowledge, the risk of cause-specific mortality has not previously been investigated in relation to CNS tumour type, years from diagnosis or diagnosis era within TYA CNS tumour survivors.

The aims of this large population-based study are to: 1) determine the risks of specific causes of death occurring among 5-year survivors of TYA CNS tumours diagnosed aged 15-39 years; 2) investigate the extent to which these risks vary according to CNS tumour type, years from diagnosis and diagnosis era.

4.3 METHODS

4.3.1 The Teenage and Young Adult Cancer Survivor Study

The Teenage and Young Adult Cancer Survivor Study (TYACSS) is to our knowledge the largest population-based cohort study to investigate the risks of adverse health outcomes in cancer survivors diagnosed age 15-39 years. The cohort consists of 200,945 5-year survivors of cancer diagnosed in England and Wales between 1971 and 2006. Of these survivors, 17,280 were 5-year survivors of a CNS tumour (including malignant, benign and unspecified tumours). The cohort was ascertained through the Office for National Statistics and the Welsh Cancer Registry. Ethical approval was provided by the National Research Ethics Service (ref:

16/LO/0895) and permission to process information without individual consent by the National Information Governance Board (NIGB) for Health and Social Care (ref: 3-03(c)2010).

4.3.2 Ascertainment of deaths

Record linkage was undertaken with the national population-based death register which is maintained by the National Health Service Digital (NHS-Digital). Linkage to NHS-Digital provided automatic notification of vital status, date of death, cause of death or date of emigration. The underlying cause of death was provided coded using the appropriate revision of the International Classification of Diseases (ICD) applicable to the year in which the death occurred [185-187].

4.3.3 CNS tumour classification

Grouping of CNS tumours was based on the internationally acknowledged classification scheme for tumours diagnosed in adolescence and young adulthood[6, 13], with some modifications to produce finer groups. Groupings used were: glial tumours, embryonal tumours, craniopharyngioma, other pituitary tumours, meningioma, ependymoma, other specified tumours and other unspecified tumours (see Table 4.1). Glial tumours were categorised according to grade (grade I, grade II, high grade [grade III & IV], and non-specific grade) based on the 2007 World Health Organisation (WHO) classification of tumours of the central nervous system (Table 4.2)[188].

4.3.4 Statistical analysis

Follow-up of individuals started at date of 5-year survival and ended at the date of the earliest of the following events: death, loss to follow-up or study end date, 28th February 2014. Standardised mortality ratios (SMRs) were calculated as the ratio of the observed number of deaths over the expected number of deaths. The expected number of deaths was derived by multiplying age (5-year band), sex and calendar-year (1-year band) specific mortality rates for the English and Welsh general population with the corresponding person-years accumulated in the cohort. Absolute excess risks (AERs) were used to provide a measure of the absolute excess number of deaths observed compared to that expected from general population. AERs were calculated as the observed minus the expected number of deaths divided by the person-years at risk and multiplied by 10,000. In what follows we often do not specify the person-years at risk, however this is always per 10,000 person-years. For each cause of death with at least 75 observed deaths SMRs and AERs were stratified by CNS tumour type. For each specific CNS tumour type, SMRs and AERs were further stratified by era of diagnosis and years from diagnosis for each cause of death with at least 30 deaths. The simultaneous influences of these factors were analysed using multivariable Poisson regression to derive relative risks (RR) and excess mortality ratios (EMRs)[154]. The RR can be interpreted as the ratio of the SMRs adjusting for other potential explanatory factors included in the model and the EMR can be interpreted as the ratio of the AERs adjusting for other potential explanatory factors included within the model. Tests of linear trend in risk across levels of a factor (e.g. era of diagnosis: 1971-1979, 1980-1989, ≥1990) were conducted using likelihood ratio tests comparing the deviance of a model containing the factor of interest (coded with the median value of variable at each level) with the deviance of a model not including the factor of interest.

Cumulative mortality by years from 5-year survival was calculated for the following causes of death: all causes, neoplastic causes, all non-neoplastic causes, respiratory disease, strokes and cardiac disease. Deaths due to causes other than the cause of interest were treated as competing risks. The expected cumulative mortality was derived from mortality rates from the general population, for each specified cause of death, using the Ederer II method [189]. All statistical analyses were conducted in Stata statistical software, version 13.1. A 2-sided p-value <0.05 was considered statistically significant for all analyses.

4.4 RESULTS

4.4.1 Cohort characteristics

Overall 17,280 5-year survivors of a CNS tumour diagnosed aged 15-39 years were included in the analysis, contributing 231,420 person-years of follow-up. The mean length of follow-up from 5-year survival was 13.4 years (range: 0-38 years) with 2,450 individuals followed for 25 years or more. Glial tumours (n=5,113; 30%) and other pituitary tumours (n=3,907; 23%) accounted for the majority of CNS tumour types within the cohort (Table 4.1). In total, 4,099 deaths were observed—the most common causes of death were: neoplastic (n=3194), stroke (n=153), cardiac disease (n=144), respiratory disease (n=141), external causes (n=97) and nervous system disease (n=95) (Table 4.3). The specific coding of nervous system diseases and respiratory diseases as underlying causes of death are provided in Table 4.4 & 4.5.

4.4.2 Cause-specific mortality among CNS tumour survivors

CNS tumour survivors experienced 7-fold the number of deaths expected from the general population (SMR=6.6, 95% confidence interval [CI] =6.4-6.8); corresponding to 150 excess

deaths (AER=150.4; CI=145.0-155.8) (Table 4.3). The risk of death was greatest in relation to neoplastic causes (which includes recurrence, metastases and subsequent primary neoplasms) with an SMR of 13; corresponding to an AER of 127 excess deaths (SMR=13.0, CI=12.5-13.4; AER=127.4, CI=122.6-132.2). With regards to specific non-neoplastic causes of death, survivors were at a substantially increased risk (SMR≥3) of death due to congenital disorder (SMR=11.2, CI=8.2-15.0), stroke (SMR=5.5, CI=4.7-6.5), 'other circulatory disease' (SMR=5.2, CI=4.0-6.6) nervous system disease (SMR=4.7, CI=3.8-5.8), genitourinary disease (SMR=4.0, CI=2.4-6.3), endocrine disease (SMR=3.8, CI=2.7-5.3) and respiratory diseases (SMR=3.4, CI=2.8-4.0) (Table 4.3).

4.4.3 Cause-specific mortality among glial tumour survivors

Survivors of glial tumours experienced a 21-fold risk of death compared to the general population; corresponding to an AER of 440 excess deaths (SMR=21.3, CI=20.4-22.1; AER=440.2, CI=421.8-458.6) (Table 4.6). Glial tumours survivors experienced the greatest multiplicative excess risk of death due to neoplasms, stroke, nervous system disease and respiratory disease with SMRs of 53.3, 11.3, 8.1 and 7.1, respectively. The number of excess deaths due to neoplastic causes increased significantly from 1971 to 2006 ($P_{trend}<0.001$), with AERs (% of total AER) of 207 (84%), 339 (90%) and 565 (96%) for survivors of a glial tumour diagnosed in 1971-1979, 1980-1989 and 1990-2006, respectively (Table 4.7). Whereas the excess number of deaths due to strokes decreased (borderline significance $P_{trend}=0.053$) with from 1971 to 2006, with AERs (% of total AER) of 19 (8%), 12 (3%) and 3 (0.4%) for survivors diagnosed 1971-1979, 1980-1989 and 1990-2006, respectively. The AER (% of total AER) for neoplastic deaths declined significantly ($P_{trend}<0.001$) by a factor of 10 from 574 (96%) at 5-14 years from diagnosis to 52 (41%) subsequent to 25 years from

diagnosis (Table 4.8). The AER for non-neoplastic deaths increased significantly (P_{trend}<0.001) with increasing years from diagnosis. The AER (% of total AER) for non-neoplastic deaths increased from 24 (4%) to 73 (59%) from 5 to 14 years from diagnosis to beyond 25 years from diagnosis, respectively; the corresponding values for stroke were 4 (1%) to 37 (30%). The cumulative mortality due to all and neoplastic causes was 61% and 52% at 35 years from diagnosis, whereas 9% and 4% was expected (Figure 4.1). The cumulative mortality due to stroke was 2.6% at 35 years from diagnosis, 6.5-fold that expected.

Both the multiplicative and absolute excess risk of all causes of death and neoplastic causes of death increased (all P_{trend} <0.001) with glial tumour grade (Table 4.9). The AER for neoplastic deaths among survivors of both Grade II and Grade III & IV gliomas increased (all P_{trend} <0.001) from 1971 to 2006; neoplastic deaths accounted for at least 84% of the total AER across all grades and eras of diagnosis (Table 4.10). The AER for neoplastic deaths among survivors of Grade II and Grade III & IV gliomas declined with increased years from diagnosis (both P_{trend} <0.001). The AER for non-neoplastic deaths among survivors of Grade II and Grade III & IV gliomas increased with increased years from diagnosis (P_{trend}=0.012 and 0.036 respectively).

4.4.4 Cause-specific mortality among craniopharyngioma survivors

Craniopharyngioma survivors had 6-fold risk of death compared to that expected (SMR=5.5, CI=4.5-6.7); corresponding to an AER of 109 excess deaths (AER=109.2, CI=83.6-134.8) (Table 4.6). In contrast to survivors of glial tumours, survivors of craniopharyngioma had a greater number of excess deaths due to non-neoplastic causes (AER=61.1, CI=41.8-80.4) than

neoplastic causes (AER=48.1, CI=31.3-65.0). 19% of the total excess number of deaths was contributed by respiratory and nervous system diseases with AERs (% of total AER) of 10.0 (9%) and 10.7 (10%), respectively. The AER for neoplastic deaths declined (P_{trend}=0.025) with increasing years from diagnosis: the AER (% of total AER) was 62 (62%) at 5-14 years from diagnosis and 23 (18%) beyond 25 years from diagnosis (Table 4.8). The AER for non-neoplastic deaths increased (P_{trend}=0.005) with increasing years from diagnosis: the AER (% of total AER) was 37 (38%) at 5-14 years from diagnosis and 106 (82%) beyond 25 years from diagnosis (Table 4.8). The cumulative mortality due to non-neoplastic causes was 23% at 35 years from diagnosis—higher than any other tumour type—whereas only 5% was expected (Figure 4.1).

4.4.5 Cause-specific mortality among other pituitary tumour survivors

Survivors of other pituitary tumours had the lowest excess risk, both in multiplicative and absolute terms, for all-cause mortality across the different groups of CNS tumour survivors presented in Table 4.6 with a 2-fold risk of death compared to the general population; corresponding to 23 excess deaths (SMR=1.9, CI=1.7-2.1; AER=22.8, CI=17.3-28.4) (Table 4.6). As for craniopharyngioma survivors, among other pituitary tumour survivors the AER for non-neoplastic deaths (AER=15.1, CI=10.8-19.5) was greater than the AER for neoplastic deaths (AER=7.7, CI=4.3-11.1). Among other pituitary tumour survivors the AER for all causes of deaths, all non-neoplastic causes of death combined and stroke deaths declined significantly from 1971 to 2006 (each P_{trend}<0.001) (Table 4.7). The AER (% of total AER) due to all non-neoplastic causes combined declined from 47 (76%) to 1 (17%) for survivors diagnosed in 1971-1979 and 1990-2006 respectively. The AER (% of total AER) due to strokes declined from 14 (22%) to 0.4 (5%) for survivors diagnosed in 1971-1979 and 1990-

2006 respectively. The AER for non-neoplastic causes increased (P_{trend}<0.001) 13-fold from 4 prior to 15 years from diagnosis to 59 subsequent to 25 years from diagnosis (Table 4.8). Non-neoplastic causes accounted for 89% of all excess deaths subsequent to 25 years from diagnosis. The AER for cardiac disease appeared to increase from 2 prior to 15 years from diagnosis to 14 subsequent to 25 years from diagnosis, but the model did not converge and so an adjusted p-value is not available). The AER for stroke increased (P_{trend}<0.001) from 0.5 prior to 15 years from diagnosis to 17 subsequent to 25 years from diagnosis. Cardiac disease and stroke accounted for 21% and 25% of the total AER subsequent to 25 years from diagnosis, respectively. The cumulative mortality due to non-neoplastic causes was 14% at 35 years from diagnosis of a pituitary tumour whereas 6% was expected (Figure 4.1). Cumulative mortality due to cardiac disease and stroke was 3.6% and 2.9% at 35 years from diagnosis, 2- and 6-fold that expected.

4.4.6 Cause-specific mortality among meningioma survivors

Survivors of meningioma experienced three-fold the number of deaths expected (SMR=3.0, CI=2.7-3.4) which corresponded to an AER of 69 (AER=68.5, CI=57.6-79.4) (Table 4.6). This was the second lowest excess (in multiplicative and absolute terms) when compared to survivors of other types of CNS tumours (Table 4.6). Similar to glial tumour survivors most (82%) of the AER was contributed by neoplastic deaths. The AER due to all and neoplastic causes of death declined significantly (P_{trend}=0.044 and P_{trend}=0.006, respectively) from 1971 to 2006 (Table 4.7). Meningioma survivors experienced the greatest percentage of excess deaths due to neoplastic causes long-term—beyond 25 years from diagnosis 79% of all excess deaths were due to neoplasms (Table 4.8). The cumulative incidence due to neoplasms and

non-neoplastic causes was 21% and 11% at 35 years from diagnosis, whereas 7% and 8% were expected (Figure 4.1).

4.4.7 Cause-specific mortality among embryonal tumour survivors

Embryonal tumour survivors had the second highest excess mortality (both in multiplicative and absolute terms) for all causes and neoplastic deaths after glial tumour survivors (SMR=13.7, CI=11.2-16.6; AER=245.0, CI=194.5-295.6) (Table 4.6). The AER (% of total AER) for neoplastic deaths was 220 (90%). The AER for neoplastic deaths declined with years from diagnosis ($P_{trend}<0.001$): the AER (% of total AER) was 312 (97%) at 5-14 years from diagnosis and 131 (56%) beyond 25 years from diagnosis (Table 4.8). The cumulative mortality due to all and neoplastic causes was substantial at 53% and 40% at 35 years from diagnosis, whereas 8% and 3% were expected (Figure 4.1).

4.4.8 Cause-specific mortality among ependymoma survivors

Ependymoma survivors experienced 5-fold the number of deaths expected, corresponding to an AER of 120 excess deaths overall (SMR=5.4, CI=4.6-6.4; AER=120.1, CI=97.0-143.1) (Table 4.6). The AER for neoplastic deaths declined ($P_{trend}=0.031$) with increased years from diagnosis (Table 4.8). The AER (% of total AER) was 105 (87%) at 5 to 14 years from diagnosis and 53 (42%) beyond 25 years from diagnosis. The AER for non-neoplastic deaths increased ($P_{trend}=0.021$) with increased years from diagnosis. The AER (% of total AER) was 16 (13%) at 5 to 14 years from diagnosis and 73 (58%) beyond 25 years from diagnosis. Ependymoma survivors, comparable to craniopharyngioma survivors experienced the greatest cumulative mortality due to non-neoplastic causes, reaching 22% at 35 years from diagnosis, whereas 7.2% was expected (Figure 4.1).

4.5 DISCUSSION

4.5.1 Main findings

In this largest ever study of TYA CNS tumour survivors, we found that neoplasms are the leading cause of death in early follow-up within survivors of all CNS tumour types. The excess number of neoplastic deaths declined with years from diagnosis after gliomas, craniopharyngioma, embryonal tumours and ependymoma and remained constant for other pituitary tumours and meningioma. In contrast the excess number of non-neoplastic deaths increased with years from diagnosis for gliomas, craniopharyngioma, other pituitary tumours and ependymoma and remained constant for meningioma and embryonal tumours. Therefore beyond 25 years from diagnosis the majority of the excess deaths are attributable to non-neoplastic causes for survivors of gliomas (59%), craniopharyngioma (82%), other pituitary tumours (89%) and ependymoma (58%). Whereas beyond 25 years from diagnosis the majority of the excess deaths are attributable to neoplastic causes for survivors of meningioma (79%) and embryonal tumours (56%). For the majority of CNS tumours, radiotherapy will be a large contributor to the number of non-neoplastic deaths in the long-term. Meningiomas are benign tumours that are often treated with surgery alone; therefore this will reduce the risk of non-neoplastic causes of death. If the meningioma is not fully resected during surgery, the chance of recurrence is high[189]. Embryonal tumours have a high recurrence rate and may recur many years after diagnosis[190, 191]. These are potential reasons why neoplasms are still the greatest cause of excess deaths in meningioma and embryonal tumour patients who have survived beyond 25 years since diagnosis.

Of major concern is the number of excess deaths due to cardiac disease and stroke subsequent to 15 years from diagnosis of a pituitary tumour, in addition to the number of excess deaths due to stroke subsequent to 25 years from diagnosis of a glial tumour. Reassuringly, glial tumour and pituitary tumour survivors treated in 1990-2006 have a significantly decreased number of excess deaths due to strokes than survivors treated in previous decades (1971-1989); however the number of excess deaths due to cardiac disease among pituitary tumour survivors did not decrease. This reduction in stroke mortality is likely a result of reducing treatment exposures, introduction of endocrine therapy (pituitary tumours[192]) and advances in imaging and diagnostic accuracy.

4.5.2 Previous studies

The majority of previous studies have focused on individuals diagnosed with a CNS tumour before 25 years of age or have only included a small subset of the TYA age range at diagnosis [24, 25, 92, 93, 128, 135, 182-184]. The only previous cohort study investigating both neoplastic and non-neoplastic causes of mortality among a wide range of TYA CNS tumour survivors—a Finnish study of 1,135 5-year survivors of a TYA (diagnosed aged 20 to 34 years) CNS tumour—reported a significant 12.3-fold risk of all-cause mortality, 40.9-fold risk of neoplastic mortality, 2.7-fold risk of circulatory mortality and a 5.5-fold risk of respiratory mortality[23]. Our study of 17,280 5-year survivors of TYA (diagnosed aged 15 to 39 years) CNS tumours found an increased risk of all-cause (6.6-fold), neoplastic (13-fold) and non-neoplastic (2.4-fold) mortality; these risks estimates were consistently lower than observed in the Finnish cohort. The Finnish cohort used the International Classification of Childhood Cancer (ICCC)[79] to define CNS tumours among individuals aged 20-34 years; therefore we conducted additional analyses restricting our cohort to the 7,038 5-year survivors diagnosed

with a CNS tumour according to the ICCC aged 20-34 years. SMRs were comparable to the Finnish cohort for all-cause mortality (10.7-fold), circulatory mortality (2.7-fold) and respiratory mortality (5.2-fold); however neoplastic mortality remained considerably lower at 23.5-fold that expected.

To our knowledge, our study is the first to estimate the risk of cause-specific mortality stratified by CNS tumour types among TYA cancer survivors; therefore no previous study is directly comparable. In addition, we have provided the risk of cause-specific mortality stratified by diagnosis era and years from diagnosis for the first time.

4.5.3 Long-term mortality due to cardiovascular diseases

This study found that the risk of death due to stroke was increased in survivors of all CNS tumour types, particularly long-term survivors of glial tumours and pituitary tumours with 30% and 25% of all excess deaths due to stroke subsequent to 25 years from diagnosis, respectively. Cranial irradiation is associated with an increased risk of stroke among childhood CNS tumour survivors [72-74, 168, 193] and a linear dose-response relationship between cranial irradiation and the risk of cerebrovascular death has been reported [73, 74]. In addition, a study of pituitary tumour survivors diagnosed as adults has reported debulking surgery and hypothalamic disorders (i.e. hypopituitarism, Cushing's disease and acromegaly) as risk factors for stroke mortality[194]. Survivors of pituitary tumour and glial tumour treated in 1990-2006 had a reduced risk of stroke than survivors treated in 1971-1979; this may relate to initiatives to reduce the size of the radiation field and improved surgical techniques. Smaller and more focused radiation fields result in less collateral damage to normal tissues and the surrounding vasculature.

This study observed an increased risk of cardiac mortality among pituitary tumour survivors. Non-hormone secreting tumours such as pituitary adenomas are associated with hypopituitarism[195]. Hypopituitarism is associated with obesity and altered low and high density lipoproteins which are considered risk factors for cardiovascular disease [195]. The hormones secreted by functioning pituitary tumours cause conditions such as acromegaly and Cushing's disease[196]. Individuals with these conditions are at a higher risk of type II diabetes mellitus, hypertension and impaired glucose tolerance, all of which are associated with cardiovascular disease[196].

To our knowledge there are no guidelines or recommendations for stroke or cardiac disease prevention specifically for TYA CNS tumour survivors. Unlike death due to recurrent tumour/metastatic spread of TYA cancer, these non-neoplastic deaths are more than likely preventable with surveillance and regular clinical follow-up, thus in particular glial tumour and other pituitary tumour survivors treated in earlier decades (1971-1989) should be considered for surveillance of risk factors for cardiovascular disease.

4.5.4 Long-term mortality due to neoplastic causes

This study observed an increase in the number of excess neoplastic deaths from 1971-1979 to 1990-2006 within glial tumour survivors. Possible explanations for this increase include: 1) death due to the original tumour has been postponed a few years by improvements in initial survival from newer treatment regimens[5]; 2) CNS tumour classifications have been refined and modified over time [188]; and 3) diagnostic accuracy and imaging have improved

dramatically since the earliest cohort, therefore it is possible a larger proportion of gliomas are being diagnosed than in the 1970s and 1980s[197].

4.5.5 Limitations of the study

The lack of detailed treatment information may be a potential limitation of the study. However by stratifying by CNS tumour type and diagnosis era we have attempted to identify individuals who are a particularly increased risk of mortality. To overcome a lack of treatment information in the current study nested case-control studies with detailed treatment information to address dose-response relationships are needed. Another limitation is the lack of potential explanatory factors such as smoking, alcohol intake and co-morbidities which may be associated with an increased risk of mortality.

4.6 CONCLUSIONS

In conclusion, this largest ever study of TYA cancer survivors has identified an excess mortality due to both neoplastic and non-neoplastic causes within survivors of CNS tumours. Of major concern is the increased mortality due to strokes in long-term survivors of glial and pituitary tumours; in addition to the increased mortality due to cardiac diseases in long-term survivors of pituitary tumours. These non-neoplastic deaths are likely to be preventable with appropriate clinical follow-up and focus should be on preventing these deaths. The risk estimates provided begin to address the gap in knowledge regarding adverse health outcomes among TYA tumour survivors, an area made a priority by the Department of Health, the National Institute for Health and Clinical Excellence and the National Cancer Research Institute [145-147].

Table 4.1: Distribution of CNS tumour type according to age at diagnosis

	All ages		15-24 years		25-39 years	
	N	%	N	%	N	%
Glial Tumours[1]	5,113	29.6	1,515	33.0	3,598	28.4
Grade I	425	9.3	267	17.6	158	4.4
Grade II	3,216	62.9	873	57.6	2,343	65.1
Grade III & IV	556	10.9	107	7.1	449	12.5
Uncertain Grade	916	17.9	268	17.7	648	18.0
Other Pituitary Tumour[2]	3,907	22.6	898	19.6	3,009	23.7
Meningioma	2,264	13.1	253	5.5	2,011	15.9
Embryonal Tumours[3]	326	1.9	157	3.4	169	1.3
Ependymoma	757	4.4	239	5.2	518	4.1
Craniopharyngioma	483	2.8	213	3.4	270	2.1
Other Specified[4]	3,139	18.2	886	19.3	2,253	17.8
Other Unspecified[5]	1,291	7.5	428	9.3	863	6.8
TOTAL	17,280	100	4,589	100	12,691	100

[1]For Glial Tumours, this category consists of pilocytic astrocytoma, other specified astrocytoma, glioblastoma, anaplastic astrocytoma, astrocytoma not otherwise specified, oligodendrogliomas, other specified glioma and glioma not otherwise specified. Glial tumours have been further categorised based on the WHO classification of tumours of the central nervous system, percentages for glial grade are percentages of total glial tumours.
[2]For Pituitary Tumour, this category consists of tumours of the pituitary (primarily pituitary adenomas), excluding craniopharyngioma
[3]For Embryonal Tumours, this category consists of medulloblastoma and supratentorial PNET
[4]For Other specified, this category consists of pineal tumours, choroid plexus tumours, CNS nerve sheath tumours. germ cell intracranial tumours and other specified CNS tumours
[5]For Other unspecified, this category consists of unspecified malignant CNS tumours and unspecified benign CNS tumours.

Table 4.2: Glial tumours according to the 2007 WHO classification of tumours of the central nervous system[188]

WHO Grade	Tumour Description	Number of 5-year survivors (%)
Grade I	Subependyoma	33
	Subependymal giant cell astrocytoma	24
	Dysembryoplastic neuroepithelial tumour	4
	Pilocytic astrocytoma	364
	Total	425
Grade II	Mixed Glioma	192
	Astrocytoma, NOS (Diffuse Glioma)	2,016
	Protoplasmic astrocytoma	31
	Gemistocytic astrocytoma	74
	Fibrillary astrocytoma	143
	Pleomorphic xanthoastrocytoma	9
	Choroid glioma	4
	Oligodendroglioma, NOS	747
	Total	3,216
Grade III & IV	Anaplastic astrocytoma	205
	Glioblastoma, NOS	244
	Giant cell glioblastoma	8
	Gliosarcoma	4
	Anaplastic oligodendroglioma	95
	Total	556
Non-specific	Glioma, NOS	833
	Oligodendroblastoma	18
	Astroblastoma	65
	Total	916

Abbreviations: NOS – not otherwise specified
[†]One individual had morphology code 9421/3-decision coded to grade I
[‡]Polar spongioblastoma does not appear in WHO classification – decision coded to grade II & IV

Table 4.3: Cause-specific excess risks of death, standardised mortality ratios (SMRs) and absolute excess risks (AERs), among survivors of all CNS tumours combined

Cause of Death	**O/E**	**SMR (95%CI)**	**AER (95% CI)**
All Causes	4099/618.2	6.6 (6.4,6.8)	150.4 (145.0,155.8)
Neoplastic Causes	3194/246.2	13.0 (12.5,13.4)	127.4 (122.6,132.2)
Non-Neoplastic Causes	905/372.0	2.4 (2.3,2.6)	23.0 (20.5,25.6)
Stroke	153/27.8	5.5 (4.7,6.5)	5.4 (4.4,6.5)
Cardiac Disease	144/110.3	1.3 (1.1,1.5)	1.5 (0.4,2.5)
Respiratory Disease	141/42.0	3.4 (2.8,4.0)	4.3 (3.3,5.3)
External Causes	97/64.4	1.5 (1.2,1.8)	1.4 (0.6,2.2)
Nervous System Disease	95/20.2	4.7 (3.8,5.8)	3.2 (2.4,4.1)
Other Circulatory Disease	67/12.9	5.2 (4.0,6.6)	2.3 (1.6,3.0)
Digestive Disease	57/48.5	1.2 (0.9,1.5)	0.4 (-0.3,1.0)
Congenital Disorder	45/4.0	11.2 (8.2,15.0)	1.8 (1.2,2.3)
Endocrine Disease	37/9.6	3.8 (2.7,5.3)	1.2 (0.7,1.7)
Infection	21/8.2	2.6 (1.6,3.9)	0.6 (0.2,0.9)
Genitourinary Disease	19/4.7	4.0 (2.4,6.3)	0.6 (0.2,1.0)
Muscoskeletal Disease	12/4.4	2.7 (1.4,4.8)	0.3 (0.0,0.6)
Other	8/4.7	1.7 (0.7,3.4)	0.1 (-0.1,0.4)
Mental Disorder	6/8.7	0.7 (0.3,1.5)	-0.1 (-0.3,0.1)
Blood Disease	3/1.7	1.8 (0.4,5.2)	0.1 (-0.1,0.2)

Abbreviations: O=observed, E=expected, SMR=standardised mortality ratio, AER=absolute excess risk, CI= confidence intervals

Table 4.4: Deaths due to respiratory disease by CNS tumour type

CNS Subtype	Pneumonia	COPD	Pneumonitis	Fibrosis	Other	Total
Glial Tumours	26 (53.1%)	5 (10.2%)	7 (14.3%)	2 (4.1%)	9 (18.4%)	49
Embryonal Tumours	3 (100%)	0	0	0	0	3
Craniopharyngioma	4 (44.4%)	2 (22.2%)	1 (11.1%)	0	2 (22.2%)	9
Other Pituitary Tumours	14 (60.9%)	4 (17.4%)	2 (8.7%)	0	3 (13.0%)	23
Meningioma	7 (35.0%)	4 (20.0%)	3 (15%)	1 (5.0%)	5 (25.0%)	20
Ependymoma	4 (44.4%)	1 (11.1%)	0	0	4 (44.4%)	9
Other Specified	8 (47.1%)	3 (17.6%)	2 (11.8%)	0	4 (23.5%)	17
Other Unspecified	4 (36.4%)	2 (18.2%)	5 (45.5%)	0	0	11
Total	80 (49.7%)	21 (14.9%)	20 (14.2%)	3 (2.1%)	27 (19.2%)	141

Table 4.5: Deaths due to nervous system disease by CNS tumour type

CNS Subtype	Meningitis	Hydrocephalus	Degenerative Disease	Motor Neuron Disease	Multiple Sclerosis	Paralytic Syndromes	Epilepsy	Other	Total
Glial Tumours	1 (3.2%)	0	1 (3.2%)	3 (9.7%)	3 (9.7%)	1 (3.2%)	18 (58.1%)	4 (12.9%)	31
Embryonal Tumours	0	0	0	0	0	0	0	0	0
Craniopharyngioma	0	1 (11.1%)	2 (22.2%)	0	0	0	5 (55.6%)	1 (11.1%)	9
Other Pituitary Tumours	0	1 (10.0%)	2 (20.0%)	0	2 (20.0%)	0	3 (30.0%)	2 (20.0%)	10
Meningioma	0	0	0	0	2 (18.2%)	2 (18.2%)	6 (54.6%)	1 (9.1%)	11
Ependymoma	1 (14.3%)	1 (14.3%)	0	0	1 (14.3%)	2 (28.6%)	0	2 (28.6%)	7
Other Specified	1 (8.3%)	0	1 (8.3%)	4 (33.3%)	1 (8.3%)	0	1 (8.3%)	4 (33.3%)	12
Other Unspecified	0	2 (13.3%)	1 (6.7%)	0	2 (13.3%)	0	10 (66.7%)	0	15
Total	3 (3.2%)	5 (5.3%)	7 (7.4%)	7 (7.4%)	11 (11.6%)	5 (5.3%)	43 (45.3%)	14 (14.7%)	95

Table 4.6: Risk of specific causes of death by CNS tumour type

Primary Diagnosis	Cause of Death	O/E	SMR (95%CI)	AER (95%CI)	%of Total AER
Glial Tumour	All Causes	2423/113.9	21.3 (20.4,22.1)	440.2 (421.8,458.6)	100%
	Neoplasm	2184/41.0	53.3 (51.0,55.5)	408.5 (391.1,426.0)	93%
	Non-Neoplastic	239/72.9	3.3 (2.9,3.7)	31.7 (25.9,37.4)	7%
	Respiratory	49/6.9	7.1 (5.2,9.3)	8.0 (5.4,10.6)	*2%*
	Stroke	54/4.8	11.3 (8.5,14.7)	9.4 (6.6,12.1)	*2%*
	Cardiac Disease	20/20.5	1.0 (0.6,1.5)	-0.1 (-1.8,1.6)	*0%*
	Nervous System	31/3.8	8.1 (5.5,11.5)	5.2 (3.1,7.3)	*1%*
	External Causes	30/16.0	1.9 (1.3,2.7)	2.7 (0.6,4.7)	*1%*
Craniopharyngioma	All Causes	104/18.9	5.5 (4.5,6.7)	109.2 (83.6,134.8)	100%
	Neoplasm	45/7.5	6.0 (4.4,8.0)	48.1 (31.3,65.0)	44%
	Non-Neoplastic	59/11.4	5.2 (3.9,6.7)	61.1 (41.8,80.4)	56%
	Respiratory	9/1.2	7.3 (3.3,13.9)	10.0 (2.4,17.5)	*9%*
	Stroke	5/0.8	6.1 (2.0,14.2)	5.4 (-0.3,11.0)	*5%*
	Cardiac Disease	8/3.3	2.5 (1.1,4.8)	6.1 (-1.0,13.2)	*6%*
	Nervous System	9/0.6	14.4 (6.6,27.3)	10.7 (3.2,18.3)	*10%*
	External Causes	7/2.2	3.2 (1.3,6.6)	6.2 (-0.5,12.8)	*6%*
Other Pituitary	All Causes	291/153.9	1.9 (1.7,2.1)	22.8 (17.3,28.4)	100%
Tumours	Neoplasm	110/63.8	1.7 (1.4,2.1)	7.7 (4.3,11.1)	34%
	Non-Neoplastic	181/90.1	2.0 (1.7,2.3)	15.1 (10.8,19.5)	66%
	Respiratory	23/10.2	2.2 (1.4,3.4)	2.1 (0.6,3.7)	*9%*
	Stroke	30/6.9	4.4 (2.9,6.2)	3.9 (2.1,5.6)	*17%*
	Cardiac Disease	49/26.1	1.9 (1.4,2.5)	3.8 (1.5,6.1)	*17%*
	Nervous System	10/5.1	2.0 (0.9,3.6)	0.8 (-0.2,1.8)	*4%*
	External Causes	13/14.6	0.9 (0.5,1.5)	-0.3 (-1.5,0.9)	*-1%*
Meningioma	All Causes	339/112.0	3.0 (2.7,3.4)	68.5 (57.6,79.4)	100%
	Neoplasm	236/49.4	4.8 (4.2,5.4)	56.3 (47.2,65.4)	82%
	Non-Neoplastic	103/62.6	1.6 (1.3,2.0)	12.2 (6.2,18.2)	18%
	Respiratory	20/8.4	2.4 (1.4,3.7)	3.5 (0.8,6.1)	*5%*
	Stroke	14/5.5	2.6 (1.4,4.3)	2.6 (0.4,4.8)	*4%*
	Cardiac Disease	20/19.1	1.0 (0.6,1.6)	0.3 (-2.4,2.9)	*0%*
	Nervous System	11/3.6	3.1 (1.5,5.5)	2.2 (0.3,4.2)	*3%*
	External Causes	9/7.9	1.1 (0.5,2.1)	0.3 (-1.5,2.1)	*0%*
Embryonal Tumour	All Causes	105/7.7	13.7 (11.2,16.6)	245.0 (194.5,295.6)	100%
	Neoplasm	90/2.6	35.0 (28.2,43.1)	220.1 (173.3,266.9)	90%
	Non-Neoplastic	15/5.1	2.9 (1.6,4.9)	24.9 (5.8,44.0)	10%
	Respiratory	3/0.4	6.8 (1.4,19.9)	6.4 (-2.1,15.0)	*3%*
	Stroke	4/0.3	12.9 (3.5,33.0)	9.3 (-0.6,19.2)	*4%*
	Cardiac Disease	1/1.3	0.7 (0.0,4.1)	-0.9 (-5.8,4.1)	*0%*
	Nervous System	0/0.3	0.0 (.,14.0)	-0.7 (-0.7,-0.7)	*0%*
	External Causes	2/1.3	1.6 (0.2,5.7)	1.9 (-5.1,8.8)	*1%*
Ependymoma	All Causes	156/28.7	5.4 (4.6,6.4)	120.1 (97.0,143.1)	100%
	Neoplasm	108/10.5	10.3 (8.5,12.5)	92.0 (72.8,111.2)	77%
	Non-Neoplastic	48/18.3	2.6 (1.9,3.5)	28.1 (15.2,40.9)	23%
	Respiratory	9/1.9	4.8 (2.2,9.1)	6.7 (1.2,12.3)	*6%*
	Stroke	6/1.2	4.9 (1.8,10.6)	4.5 (-0.0,9.0)	*4%*
	Cardiac Disease	9/5.8	1.6 (0.7,3.0)	3.0 (-2.5,8.6)	*3%*
	Nervous System	7/0.9	7.8 (3.1,16.1)	5.8 (0.9,10.6)	*5%*
	External Causes	3/3.4	0.9 (0.2,2.6)	-0.4 (-3.6,2.8)	*0%*
Other	All Causes	681/183.1	3.7 (3.4,4.0)	78.5 (70.4,86.5)	100%
	Neoplasm	421/71.4	5.9 (5.3,6.5)	55.1 (48.8,61.4)	70%
	Non-Neoplastic	260/111.7	2.3 (2.1,2.6)	23.4 (18.4,28.4)	30%
	Respiratory	28/12.8	2.2 (1.5,3.2)	2.4 (0.8,4.0)	*3%*
	Stroke	40/8.3	4.8 (3.5,6.6)	5.0 (3.0,7.0)	*6%*
	Cardiac Disease	37/34.3	1.1 (0.8,1.5)	0.4 (-1.4,2.3)	*1%*
	Nervous System	27/5.9	4.6 (3.0,6.7)	3.3 (1.7,4.9)	*4%*
	External Causes	33/18.9	1.7 (1.2,2.5)	2.2 (0.4,4.0)	*3%*

Abbreviations: O=observed, E=expected, SMR=standardised mortality ratio, AER=absolute excess risk, CI= confidence intervals

†Other consists of other specified and other unspecified tumour types

Table 4.7: Absolute excess risk of specific causes of death by CNS tumour type and era of diagnosis

CNS Tumour Type Cause of Death	1971-1979			1980-1989			1990-2006			
	O/E	**AER**	**%of Total AER**	**O/E**	**AER**	**%of Total AER**	**O/E**	**AER**	**%of Total AER**	**P_{trend}***
Glial Tumours										
All Causes	312/39.8	247.4 (216.0,278.9)	100%	753/42.5	376.2 (347.7,404.6)	100%	1358/31.6	587.7 (555.7,619.7)	100%	<0.001
Neoplasm	244/16.1	207.1 (179.3,235.0)	84%	656/15.6	339.0 (312.5,365.6)	90%	1284/9.2	564.9 (533.7,596.0)	96%	<0.001
Non-Neoplastic	68/23.7	40.3 (25.6,55.0)	16%	97/26.9	37.1 (26.9,47.4)	10%	74/22.4	22.9 (15.4,30.3)	4%	0.348
Respiratory Disease	14/3.0	10.0 (3.4,16.7)	*4%*	17/2.6	7.6 (3.4,11.9)	*2%*	18/1.4	7.3 (3.7,11.0)	*1%*	0.620
Stroke	23/1.9	19.2 (10.7,27.7)	*8%*	24/1.8	11.8 (6.7,16.9)	*3%*	7/1.1	2.6 (0.3,4.9)	*0%*	0.053
Nervous System Disease	8/1.2	6.2 (1.2,11.3)	*3%*	13/1.4	6.1 (2.4,9.9)	*2%*	10/1.2	3.9 (1.1,6.6)	*1%*	0.697
External Causes	7/3.3	3.3 (-1.4,8.0)	*1%*	8/5.8	1.2 (-1.8,4.1)	*0%*	15/6.8	3.6 (0.3,7.0)	*1%*	0.093
Craniopharyngioma										
All Causes	34/8.2	111.3 (61.9,160.7)	100%	46/7.1	125.9 (82.9,168.9)	100%	24/3.5	85.6 (45.4,125.7)	100%	0.240
Neoplasm	15/3.5	49.6 (16.8,82.4)	45%	20/2.8	55.7 (27.3,84.0)	44%	10/1.2	36.9 (11.0,62.8)	43%	0.099
Non-Neoplastic	19/4.7	61.7 (24.8,98.7)	55%	26/4.3	70.2 (37.9,102.6)	56%	14/2.4	48.6 (18.0,79.3)	57%	0.900
Other Pituitary Tumours										
All Causes	95/39.8	62.2 (40.7,83.8)	100%	128/69.9	24.7 (15.3,34.1)	100%	68/44.2	8.6 (2.8,14.5)	100%	<0.001
Neoplasm	31/17.6	15.1 (2.8,27.4)	24%	43/30.0	5.5 (0.1,11.0)	22%	36/16.2	7.2 (2.9,11.4)	83%	0.068
Non-Neoplastic	64/22.2	47.1 (29.5,64.8)	76%	85/39.8	19.2 (11.5,26.9)	78%	32/28.1	1.4 (-2.6,5.4)	17%	<0.001
Cardiac Disease	16/7.9	9.1 (0.3,17.9)	*15%*	24/12.1	5.1 (1.0,9.1)	*20%*	9/6.1	1.1 (-1.1,3.2)	*12%*	0.123
Stroke	14/2.0	13.5 (5.2,21.8)	*22%*	13/3.1	4.2 (1.2,7.2)	*17%*	3/1.8	0.4 (-0.8,1.7)	*5%*	<0.001
Meningioma										
All Causes	116/48.1	80.4 (55.4,105.4)	100%	134/40.9	78.6 (59.4,97.7)	100%	89/23.1	51.4 (37.0,65.8)	100%	0.044
Neoplasm	80/21.5	69.2 (48.5,90.0)	86%	95/18.8	64.3 (48.2,80.4)	82%	61/9.1	40.4 (28.5,52.4)	79%	0.006
Non-Neoplastic	36/26.6	11.2 (-2.7,25.1)	14%	39/22.1	14.3 (3.9,24.6)	18%	28/14.0	10.9 (2.9,19.0)	21%	0.227
Embryonal Tumours										
All Causes	21/2.9	197.1 (99.1,295.2)	100%	37/2.6	248.6 (162.5,334.6)	100%	47/2.2	268.3 (187.9,348.7)	100%	0.709
Neoplasm	15/1.1	151.3 (68.4,234.1)	77%	31/0.8	217.7 (138.9,296.5)	88%	44/0.6	259.8 (182.0,337.6)	97%	0.908
Non-Neoplastic	6/1.8	45.9 (-6.5,98.3)	23%	6/1.7	30.9 (-3.7,65.6)	12%	3/1.6	8.5 (-11.8,28.8)	3%	0.521
Ependymoma										
All Causes	54/11.9	168.4 (110.8,225.9)	100%	47/10.1	100.8 (64.2,137.5)	100%	55/6.8	108.7 (75.9,141.5)	100%	0.104
Neoplasm	31/4.7	105.0 (61.4,148.6)	62%	36/3.7	88.1 (56.0,120.2)	87%	41/2.0	87.9 (59.6,116.2)	81%	0.123
Non-Neoplastic	23/7.1	63.4 (25.8,101.0)	38%	11/6.3	12.8 (-5.0,30.5)	13%	14/4.8	20.8 (4.2,37.3)	19%	0.735
Other†										
All Causes	192/76.1	76.0 (58.2,93.8)	100%	243/62.2	85.8 (71.3,100.3)	100%	246/44.8	74.2 (62.8,85.5)	100%	0.019
Neoplasm	102/31.7	46.1 (33.1,59.1)	61%	155/25.4	61.5 (49.9,73.1)	72%	164/14.3	55.2 (45.9,64.4)	74%	0.047
Non-Neoplastic	90/44.4	29.9 (17.7,42.1)	39%	88/36.8	24.3 (15.6,33.0)	28%	82/30.4	19.0 (12.5,25.5)	26%	0.199

Abbreviations: O=observed, E=expected, AER=absolute excess risk, CI= confidence intervals.
*Adjusting for attained age, age at diagnosis and sex.
†Other consists of other specified and other unspecified tumour types

Table 4.8: Absolute excess risk of specific causes of death by CNS tumour type and years from diagnosis

CNS Tumour Type Cause of Death	5-14 years from diagnosis			15-24 years from diagnosis			25+ years from diagnosis			
	O/E	**AER**	**%of Total AER**	**O/E**	**AER**	**%of Total AER**	**O/E**	**AER**	**%of Total AER**	**P_{trend}***
Glial Tumours										
All Causes	2021/44.0	597.6 (571.0,624.3)	100%	295/35.0	191.4 (166.6,216.2)	100%	107/34.9	124.4 (89.4,159.4)	100%	<0.001
Neoplasm	1910/12.7	573.5 (547.6,599.4)	96%	229/13.1	158.9 (137.1,180.8)	83%	45/15.1	51.5 (28.9,74.2)	41%	<0.001
Non-Neoplastic	111/31.3	24.1 (17.9,30.3)	4%	66/21.9	32.5 (20.8,44.2)	17%	62/19.8	72.8 (46.2,99.5)	59%	<0.001
Respiratory Disease	25/1.9	7.0 (4.0,9.9)	*1%*	16/2.0	10.3 (4.5,16.1)	*5%*	8/3.0	8.6 (-1.0,18.2)	*7%*	0.395
Stroke	16/1.7	4.3 (1.9,6.7)	*1%*	15/1.5	9.9 (4.3,15.5)	*5%*	23/1.5	37.0 (20.8,53.2)	*30%*	<0.001
Nervous System Disease	18/1.7	4.9 (2.4,7.5)	*1%*	3/1.1	1.4 (-1.1,3.9)	*1%*	10/1.1	15.4 (4.7,26.1)	*12%*	0.160
External Causes	16/10.3	1.7 (-0.6,4.1)	*0%*	9/4.1	3.6 (-0.7,8.0)	*2%*	5/1.7	5.7 (-1.8,13.3)	*5%*	0.001
Craniopharyngioma										
All Causes	46/5.3	98.9 (66.6,131.2)	100%	35/6.5	116.4 (69.0,163.8)	100%	23/7.1	129.4 (52.8,205.9)	100%	0.510
Neoplasm	27/1.7	61.5 (36.8,86.2)	62%	12/2.6	38.2 (10.5,66.0)	33%	6/3.2	23.0 (-16.1,62.1)	18%	0.025
Non-Neoplastic	19/3.6	37.4 (16.7,58.2)	38%	23/3.9	78.2 (39.7,116.6)	67%	17/3.9	106.4 (40.6,172.2)	82%	0.005
Other Pituitary Tumours										
All Causes	99/49.0	14.6 (8.9,20.2)	100%	103/59.4	22.7 (12.4,33.1)	100%	89/45.4	66.8 (38.5,95.2)	100%	0.005
Neoplasm	52/17.2	10.1 (6.0,14.3)	70%	32/25.6	3.4 (-2.4,9.1)	15%	26/21.0	7.6 (-7.7,22.9)	11%	0.210
Non-Neoplastic	47/31.8	4.4 (0.5,8.3)	30%	71/33.8	19.4 (10.8,28.0)	85%	63/24.4	59.2 (35.3,83.1)	89%	<0.001
Cardiac Disease	14/7.5	1.9 (-0.2,4.0)	*13%*	18/10.6	3.9 (-0.5,8.2)	*17%*	17/8.1	13.7 (1.3,26.1)	*21%*	-[¥]
Stroke	4/2.2	0.5 (-0.6,1.7)	*4%*	13/2.6	5.4 (1.7,9.1)	*24%*	13/2.1	16.8 (5.9,27.6)	*25%*	<0.001
Meningioma										
All Causes	156/31.8	66.6 (53.5,79.7)	100%	101/39.1	62.1 (42.3,81.8)	100%	82/41.2	90.9 (51.4,130.4)	100%	0.889
Neoplasm	122/12.6	58.7 (47.0,70.3)	88%	63/18.0	45.1 (29.5,60.7)	73%	51/18.9	71.5 (40.4,102.7)	79%	0.298
Non-Neoplastic	34/19.2	7.9 (1.8,14.1)	12%	38/21.1	16.9 (4.8,29.0)	27%	31/22.3	19.4 (-4.9,43.7)	21%	0.412
Embryonal Tumours										
All Causes	79/2.8	320.2 (247.0,393.3)	100%	13/2.5	92.4 (30.1,154.8)	100%	13/2.4	232.1 (78.0,386.1)	100%	0.011
Neoplasm	75/0.7	312.1 (240.8,383.4)	97%	8/0.9	62.8 (13.9,111.7)	68%	7/1.0	131.1 (18.1,244.1)	56%	<0.001
Non-Neoplastic	4/2.1	8.1 (-8.4,24.5)	3%	5/1.6	29.6 (-9.1,68.2)	32%	6/1.4	101.0 (-3.7,205.6)	44%	0.076
Ependymoma										
All Causes	83/9.0	120.1 (91.1,149.1)	100%	47/10.0	117.3 (74.8,159.9)	100%	26/9.8	126.4 (48.6,204.1)	100%	0.681
Neoplasm	67/2.6	104.6 (78.6,130.7)	87%	30/3.7	83.2 (49.2,117.2)	71%	11/4.2	53.1 (2.5,103.7)	42%	0.031
Non-Neoplastic	16/6.5	15.5 (2.8,28.2)	13%	17/6.2	34.1 (8.5,59.7)	29%	15/5.6	73.3 (14.2,132.4)	58%	0.021
Other[†]										
All Causes	385/54.6	90.7 (80.1,101.2)	100%	186/60.6	67.1 (52.8,81.4)	100%	110/67.9	50.6 (25.9,75.3)	100%	<0.001
Neoplasm	275/17.1	70.8 (61.8,79.7)	78%	94/24.5	37.2 (27.0,47.4)	55%	52/29.8	26.7 (9.7,43.7)	53%	<0.001
Non-Neoplastic	110/37.5	19.9 (14.3,25.5)	22%	92/36.1	29.9 (19.8,40.0)	45%	58/38.1	23.9 (6.0,41.9)	47%	0.569

Abbreviations: O=observed, E=expected, AER=absolute excess risk, CI= confidence intervals.

†Other consists of other specified and other unspecified,

* adjusted for age at diagnosis, diagnosis era and sex.

[¥]Could not converge

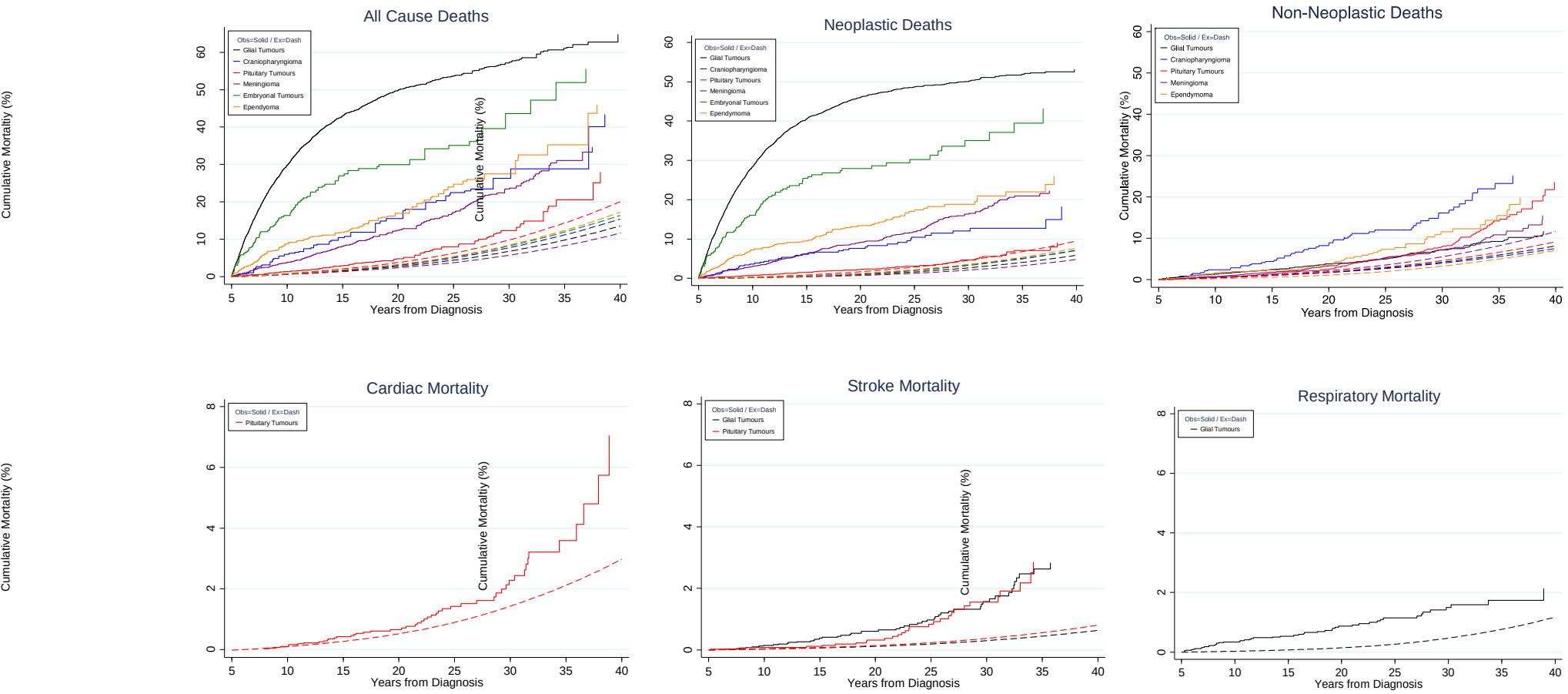


Figure 4.1: Cause-specific cumulative mortality, according to CNS tumour type, with years from diagnosis as the time scale
*Restricted to CNS tumour types with over 25 events

Table 4.9: Risk of all cause, neoplastic and non-neoplastic mortality by grade among glial tumour survivors

Cause of Death	Glial Grade	O/E	SMR (95%CI)	AER (95%CI)
All Causes	Grade I	38/5.7	6.7 (4.7,9.1)	73.0 (45.7,100.3)
	Grade II	1619/68.2	23.7 (22.6,24.9)	477.0 (452.7,501.2)
	Grade III & IV	307/8.4	36.7 (32.7,41.0)	756.7 (669.7,843.8)
	P_{trend}*		*<0.001*	*<0.001*
Neoplasm	Grade I	27/1.7	15.9 (10.5,23.1)	57.2 (34.2,80.2)
	Grade II	1480/24.3	60.9 (57.8,64.0)	447.7 (424.5,470.9)
	Grade III & IV	286/3.0	96.4 (85.6,108.3)	717.2 (633.2,801.2)
	P_{trend}*		*<0.001*	*<0.001*
Non-Neoplastic	Grade I	11/4.0	2.7 (1.4,4.9)	15.8 (1.1,30.5)
	Grade II	139/43.9	3.2 (2.7,3.7)	29.2 (22.1,36.4)
	Grade III & IV	21/5.4	3.9 (2.4,5.9)	39.5 (16.7,62.3)
	P_{trend}*		*0.171*	*0.195*

Abbreviations: O-observed, E-expected, SMR- standardised mortality ratio, AER= absolute excess risk, CI-confidence interval
*Adjusted for attained age, age at diagnosis, diagnosis era and sex

Table 4.10: Risk of all cause, neoplastic and non-neoplastic mortality by grade and era of diagnosis among glial tumour survivors

Glial Grade	Cause of Death	1971-1979			1980-1989			1990-2006			
		O/E	AER (95%CI)	%of Total AER	O/E	AER (95%CI)	%of Total AER	O/E	AER (95%CI)	%of Total AER	P_{trend}*
Grade I	All Causes	1/0.4	-	-	13/2.4	79.5 (26.7,132.3)	100%	24/3.0	70.9 (38.5,103.2)	100%	-
	Neoplasm	1/0.2	-	-	10/0.8	68.6 (22.3,114.9)	86%	16/0.7	51.5 (25.1,77.9)	73%	-
	Non-Neoplastic	0/0.2	-	-	3/1.5	10.9 (-14.4,36.3)	14%	8/2.2	19.4 (0.7,38.1)	27%	-
Grade II	All Causes	168/20.3	245.2 (203.1,287.4)	100%	509/27.7	385.5 (350.1,421.0)	100%	942/20.3	658.1 (615.1,701.0)	100%	<0.001
	Neoplasm	134/8.2	208.8 (171.1,246.5)	85%	447/10.1	350.0 (316.8,383.2)	91%	899/6.0	637.6 (595.6,679.5)	97%	<0.001
	Non-Neoplastic	34/12.0	36.5 (17.5,55.4)	15%	62/17.6	35.6 (23.2,47.9)	9%	43/14.3	20.5 (11.3,29.7)	3%	0.407
Grade III & IV	All Causes	29/3.3	267.7 (157.9,377.4)	100%	44/1.7	629.2 (435.9,822.4)	100%	234/3.5	997.4 (867.6,1127.1)	100%	<0.001
	Neoplasm	23/1.3	225.2 (127.4,322.9)	84%	40/0.6	585.1 (400.9,769.4)	93%	223/1.0	960.4 (833.8,1087.0)	96%	<0.001
	Non-Neoplastic	6/1.9	42.5 (-7.4,92.4)	16%	4/1.0	44.0 (-14.2,102.3)	7%	11/2.5	36.9 (8.8,65.1)	4%	0.100

Abbreviations: O=observed, E=expected, AER=absolute excess risk, EMR= excess mortality ratio, CI= confidence intervals
* Adjusting for attained age, age at diagnosis and sex
- Insufficient numbers to reliably estimate.

Table 4.11: Risk of all cause, neoplastic and non-neoplastic mortality by grade and years from diagnosis among glial tumour survivors

		5-14 years from diagnosis			15-24 years from diagnosis			25+ years from diagnosis			
Glial Grade	**Cause of Death**	**O/E**	**AER (95%CI)**	**%of Total AER**	**O/E**	**AER (95%CI)**	**%of Total AER**	**O/E**	**AER (95%CI)**	**%of Total AER**	**P_{trend}***
Grade I	*All Causes*	28/3.0	78.2 (45.8,110.6)	100%	9/1.8	71.2 (13.0,129.4)	100%	1/0.9	-	-	-
	Neoplasm	20/0.7	60.3 (32.9,87.7)	77%	7/0.6	63.4 (12.0,114.7)	89%	0/0.4	-	-	-
	Non-Neoplastic	8/2.3	17.9 (0.5,35.2)	23%	2/1.2	7.9 (-19.6,35.3)	11%	1/0.5	-	-	-
Grade II	*All Causes*	1361/27.6	648.6 (613.4,683.7)	100%	192/21.2	201.6 (169.5,233.7)	100%	66/19.4	133.8 (88.1,179.5)	100%	<0.001
	Neoplasm	1292/8.0	624.5 (590.2,658.8)	96%	157/7.9	176.0 (147.0,205.0)	87%	31/8.4	65.0 (33.6,96.3)	49%	<0.001
	Non-Neoplastic	69/19.6	24.0 (16.1,32.0)	4%	35/13.3	25.6 (11.9,39.3)	13%	35/11.0	68.8 (35.6,102.1)	51%	0.012
Grade III & IV	*All Causes*	281/4.1	961.1 (847.0,1075.1)	100%	19/1.9	250.0 (125.2,374.7)	100%	7/2.4	120.1 (-16.5,256.8)	100%	<0.001
	Neoplasm	270/1.1	933.0 (821.2,1044.8)	97%	13/0.7	179.1 (76.0,282.3)	72%	3/1.1	50.3 (-39.2,139.7)	42%	<0.001
	Non-Neoplastic	11/2.9	28.1 (5.5,50.6)	3%	6/1.1	70.8 (0.8,140.9)	28%	4/1.3	69.8 (-33.5,173.1)	58%	0.036

Abbreviations: O=observed, E=expected, AER=absolute excess risk, EMR= excess mortality ratio, CI= confidence intervals
* Adjusting for diagnosis era, age at diagnosis and sex
- Insufficient numbers to reliably estimate.

Chapter 5

Risk of soft-tissue sarcoma among 69,460 5-year survivors of childhood cancer in Europe

5.1 ABSTRACT

Background: Childhood cancer survivors are at increased risk of developing a subsequent primary soft-tissue sarcoma (STS), but the risks of specific STS histological subtypes is unknown. We quantified the risk of STS histological subtypes after specific types of childhood cancer.

Methods: The PanCare Childhood and Adolescent Survivor Care and Follow-up Studies consortium combined data from 13 European cohorts providing a cohort of 69,460 5-year survivors of childhood cancer. Standardised incidence ratios (SIR) and absolute excess risks (AER) were calculated to quantify the excess risk of STS.

Results: Overall, 301 STS developed compared to 19 expected (SIR=16, 95% Confidence Interval [CI]=14–18). Highest SIRs were observed for malignant peripheral nerve sheath tumours (MPNST) (SIR=41, CI=14–18), leiomyosarcoma (SIR=30, CI=24–37), and fibromatous neoplasms (SIR=12, CI=9–16). SIRs and AERs of STS did not vary significantly across different treatment decades after adjusting for other explanatory factors (P_{trend}=0.699 & 0.842). AERs for all STS subtypes were generally low at any attained age or years from diagnosis (AER<1 per 10,000 survivors per year), except for a leiomyosarcoma among retinoblastoma survivors—the AER increased with attained age and years from diagnosis reaching 53 per 10,000 survivors per year beyond 45 years from diagnosis.

Conclusion: Childhood cancer survivors are at increased risk of developing STS, particularly leiomyosarcoma, MPNSTs and fibromatous neoplasms. Whilst the observed risks relative to the general population were substantial, the absolute risk of developing any STS subtype was low, except for leiomyosarcoma after retinoblastoma. These long-term risks provide an evidence base for developing clinical follow-up guidelines.

5.2 INTRODUCTION

Within Europe, 79% of children diagnosed with cancer now survive at least 5 years [198]. This high survival has resulted in a large population of long-term survivors of childhood cancer. Childhood cancer survivors are at an increased risk of long-term adverse-health outcomes with one of the most serious being the development of a subsequent primary neoplasm (SPN)—overall risks 3 to 6-fold that expected from the general population [96, 98, 100, 104, 106, 199]. STS SPNs are highly fatal, with 5-year survival at only 19–41% after radiation-induced sarcomas [200-202].

Previous studies have shown that the risk of developing any subsequent primary soft-tissue sarcoma (STS) is substantially elevated following childhood cancer, particularly in survivors of heritable retinoblastoma and Wilms tumour [112-115, 203-205]. However, because development of a STS is rare, previous reports were based on small observed numbers and, to our knowledge, no previous study has reported risk estimates for specific histological subtypes of STS after all specific types of childhood cancer, except heritable retinoblastoma.

Due to the increased awareness of adverse health outcomes among childhood cancer survivors, recent treatments for childhood cancers with a favourable prognosis have moved towards lowering therapeutic exposures. So far, the potential impact of such lower therapeutic exposure on the risk of STS SPNs has not been investigated.

We investigated the risks of STS within a large-scale pan-European cohort of 69,460 5-year survivors of childhood cancer. The current study provides over 3-fold the number of STS provided by the largest study on STS SPN published to date which is not included in the

present study [112]. The aim of this study was to provide risk estimates for all and specific histological subtypes of STS after all and specific types of childhood cancer.

5.3 METHODS

5.3.1 The PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies (PanCareSurFup)

PanCareSurFup combines data from across Europe to form the largest collaborative study to date to investigate adverse health outcomes in long-term survivors of childhood and adolescent cancer (referred to as childhood cancer henceforth). The study comprises data from 13 European cohorts, within 12 countries, of childhood cancer survivors, with contributions from both population-based cancer registries and major treatment centres (Table 5.1). Ethical approval was obtained separately for each cohort from the appropriate bodies within each specific country.

5.3.2 Cohort ascertainment

Childhood cancers obtained were coded according to the first, second or third revisions of the International Classification of Disease for Oncology (ICD-O). To enable childhood cancers to be grouped according to the International Classification of Childhood Cancers (ICCC)[79], morphology and topography codes were converted into ICD-O-3 using the IARC/IACR Cancer Registry Tools software [152]. Childhood cancers were excluded if the associated ICD-O code was not in ICCC or was not of a malignant behaviour (except for intracranial tumours, for which "benign" and "uncertain whether benign or malignant" were included). Childhood cancers provided by the Slovenian cancer registry prior to 1983 were coded according to the International Classification of Disease (ICD) 7th edition and could not be classified according

to ICCC; however these individuals were not excluded and were grouped as "not classifiable". To ensure consistency between cohorts, individuals with Langerhans cell histiocytosis, myelodysplastic syndromes, chronic myeloproliferative and lymphoproliferative disorders or immunoproliferative diseases were excluded as these conditions were not ascertained satisfactorily by all countries (Figure 5.1). In total, the cohort consists of 69,460 5-year survivors of cancer diagnosed before the age of 20 years between 1940 and 2008 (Tables 5.1 and 5.2).

5.3.3 Subsequent primary neoplasm ascertainment

SPNs were ascertained through several different methods and the primary method of validation was obtaining pathology reports or in their absence other means of clinical diagnosis (see Table 5.1). To be included as a SPN, tumours had to have a different histological classification to that of the childhood cancer and have a malignant behaviour code—except for intracranial tumours where any behaviour code was included (Figure 5.2). The majority (70%) of affected individuals in the cohort were aged 15-39 years at diagnosis of a STS, therefore STS SPNs were classified using the adolescents and young adult (AYA) cancer classification scheme [13].

5.3.4 General population soft-tissue sarcoma rates for the derivation of expected numbers

To compare the observed number of STS SPNs with the expected numbers from the general population, general population STS incidence rates formatted according to the AYA classification (by ICD-O morphology) were required. Incidence rates by ICD-O morphology were available for the UK (years 1971-2006: England and Wales, only) [206] and Finland (years

1953-2011) [207]. For other countries we used either the UK or Finnish rates (UK for: France, Hungary, Italy, Netherlands, Slovenia and Switzerland; Finnish for: Denmark, Norway, Sweden and Iceland). When the range of calendar-years for the general population cancer rates did not extend to the ascertainment period of STS, rates from the closest available year were used.

5.3.5 Statistical analysis

Follow-up began at 5-year survival from childhood cancer and ended at the first occurrence of death, loss to follow up, or cohort exit date. Analyses involving observed and expected numbers allowed multiple STS per individual. Standardised incidence ratios (SIRs) were calculated as the observed divided by the expected number of STS. The expected number of STS was calculated by accumulating person-years in the cohort by sex, single calendar-year and 5-year age-strata and multiplying by the corresponding general population STS incidence rates. Absolute excess risks (AERs) were calculated as the observed minus the expected number of STS, divided by person-years at risk and multiplied by 10,000. The AER can be interpreted as the number of excess STS observed beyond that expected per 10,000 per year. The denominator is often not provided in the Results and Discussion as it is always 10,000 person-years. SIRs and AERs were stratified by sex, country, childhood cancer diagnosis, age at and decade of childhood cancer diagnosis, attained age, and years from childhood cancer diagnosis for STS subtypes where numbers were sufficient (n>40). The simultaneous effect of these potential explanatory factors was analysed using multivariable Poisson regression with a user-defined link function to calculate relative risks (RR) and relative excess risks (RER) [154]. RRs can be interpreted as the ratio of SIRs adjusted for other explanatory factors. RERs can be interpreted as the ratio of AERs adjusted for other explanatory factors.

Cumulative incidence of the first occurrence of a STS, treating death as a competing risk, was calculated by years since 5-year survival. Expected cumulative incidence was calculated using the Ederer II method [189]. All statistical analyses were conducted in Stata statistical software, version 14.1. A 2-sided p-value <0.05 was considered statistically significant.

5.4 RESULTS

5.4.1 Cohort characteristics

Overall, individuals contributed 1,126,424 person-years and a median follow-up of 14.5 years from 5-year survival (range: 0-62). A total of 301 STS were observed among 299 of the 69,460 5-year survivors of childhood cancer (Table 5.3). The most commonly observed STS were, leiomyosarcoma (n=80, [27%]), fibromatous neoplasms (n=55, [18%]), and malignant peripheral nerve sheath tumours (MPNST) (n=45, [15%]).

5.4.2 Overall risk of soft-tissue sarcoma

Overall, survivors had a 16-fold (95% confidence interval [CI]=14.0–17.6) risk of developing a STS compared to that expected from the general population, corresponding to an AER of 2.5 (Table 5.4). Survivors of each specific type of childhood cancer were at a significantly increased multiplicative (SIR) and absolute (AER) excess risk of developing a STS, particularly retinoblastoma survivors (SIR=72.8, CI=56.1–93.0; AER=11). The multivariable analysis revealed that there was no statistically significant relationship between age at diagnosis or decade of diagnosis (1940-2008) with the excess risk of STS in either multiplicative or absolute terms. The RR declined significantly with attained age and years from diagnosis (P_{trend}=0.002 and P_{trend}=0.001). The RER increased significantly with increasing years from diagnosis and attained age (both P_{trend}<0.001). Beyond 45 years from

diagnosis the AER was 9. The cumulative incidence of developing a STS was 1.4% (CI=1.1–1.6) at 45 years from diagnosis, whereas 0.1% was expected (Figure 5.3a).

5.4.3 Risk of leiomyosarcoma

The SIR of developing a leiomyosarcoma was 30-fold (CI=23.7–37.2) increased among survivors of childhood cancer than in the general population; corresponding to an AER of 0.7 (Table 5.5). The SIR was highest among retinoblastoma survivors (SIR=342.9, CI=245.0–466.9) and Wilms tumour survivors (SIR=74.2, CI=37.1–132.8). 77% of leiomyosarcomas observed after retinoblastoma developed outside of irradiated tissue and 87% of these retinoblastomas were known to be heritable (Table 5.6). 91% of leiomyosarcomas observed after Wilms tumour developed within irradiated tissue. SIRs were particularly high among survivors diagnosed at a young age, with almost a 100-fold increased risk of developing a leiomyosarcoma among individuals diagnosed before age 5 years; and the RR declined significantly with older age at diagnosis (P_{trend}=0.011). This relationship remained after excluding survivors of both retinoblastoma and Wilms tumour from the analysis (P_{trend}=0.016). 65% of survivors diagnosed before age 5 who developed a leiomyosarcoma had a genetic predisposition (35 RB1 mutation, 1 neurofibromatosis, 1 Li-Fraumeni syndrome). No statistically significant relationship between decade of diagnosis (1940-2008) and the excess risk of leiomyosarcoma was observed in either multiplicative or absolute terms. The RR did not vary significantly with attained age or years from diagnosis (P_{trend}=0.765 and P_{trend}=0.520). The RER increased substantially with attained age and years from diagnosis (both P_{trend}<0.001); beyond 45 years from diagnosis the AER was 9. The cumulative incidence of developing a leiomyosarcoma was 0.6% (CI=0.4–0.8) at 45 years from diagnosis, whereas 0.02% was expected (Figure 5.3b).

5.4.4 Risk of fibromatous neoplasms

Survivors had a 12-fold (CI=9.3–16.0), increased risk of developing a fibromatous SPN than that expected, corresponding to an AER of 0.4 (Table 5.7). Survivors were most at risk of fibrosarcoma (SIR=25.1, CI=16.5–36.5) and malignant fibrous histiocytoma (SIR=28.3, CI=18.3–41.7) (Table 5.3). Bone sarcoma, retinoblastoma and Hodgkin lymphoma survivors had the highest risk of developing a fibromatous SPN with SIRs of 34.5, 31.0 and 24.2, respectively (Table 5.7*)*. 83%, 57% and 57% of fibrosarcoma after retinoblastoma, bone sarcoma and Hodgkin lymphoma occurred in irradiated tissue, respectively (Table 5.6). No statistically significant relationship between age at diagnosis or decade of diagnosis (1940-2008) and the excess risk of fibromatous SPNs was observed in either multiplicative or absolute terms. RRs decreased significantly with attained age and years from diagnosis (both $P_{trend}<0.001$), whereas the RERs did not vary significantly with attained age or years from diagnosis ($P_{trend}=0.169$, $P_{trend}=0.110$, respectively). The cumulative incidence of developing a fibromatous neoplasm increased to 0.12% (CI=0.08–0.15) at 30 years from diagnosis compared to 0.01% expected (Figure 5.3c).

5.4.5 Risk of malignant peripheral nerve sheath tumours (MPNST)

MPNSTs, also known as malignant schwannoma or neurofibrosarcoma, are a rare type of STS arising from the cells that surround the nerves. The highest SIR for any STS subtype was observed for MPNST SPNs, with a 41-fold (CI=29.6–54.3) increased risk than that expected (Table 5.8); the corresponding AER was 0.4. 47% of all MPNST were associated with Neurofibromatosis. 63% and 64% of MPNST occurred within irradiated tissue among childhood cancer survivors with or without Neurofibromatosis, respectively (Table 5.9). SIRs

were highest among survivors of CNS tumours (SIR=80.5, CI=48.4–125.7), Hodgkin lymphoma (SIR=81.3, CI=35.1–160.1), and Wilms tumour (SIR=76.0, CI=27.9–165.4). No statistically significant trends in excess risks were observed in relation to years from diagnosis, attained age, age at diagnosis or decade of diagnosis (1940-2008), in multiplicative or absolute terms. The cumulative incidence of developing a nerve sheath tumour reached 0.01% (CI=0.07–0.14) at 30 years from diagnosis, whereas 0.002% was expected (Figure 5.3d).

5.4.6 Risk of soft-tissue sarcoma among retinoblastoma survivors

As survivors of retinoblastoma experienced the highest risk of developing a STS (SIR=72.8, CI=56.1–93.0), particularly leiomyosarcoma (SIR=342.9, CI=245.0–466.9), we investigated the risks by the potential explanatory factors in more detail (Table 5.10 & 5.11). The AER for STS among survivors of retinoblastoma increased substantially with increasing years from diagnosis and attained-age (P_{trend}<0.001), reaching 58 beyond 45 years from diagnosis (Table 5.10). Beyond 45 years from diagnosis, leiomyosarcomas accounted for 91% of all excess STS among retinoblastoma survivors, with an AER of 53 (Table 5.11). The cumulative incidence of developing a STS among retinoblastoma survivors was 5.4% (CI=3.7–6.9) at 45 years from diagnosis whereas 0.07% was expected (Figure 5.3a). The cumulative incidence of developing a leiomyosarcoma was 3.7% (CI=2.4–5.3) at 45 years from diagnosis, whereas 0.01% was expected (Figure 5.3b).

5.5 DISCUSSION

The PanCareSurFup cohort provides unprecedented insight into the absolute and excess risks of STS SPN after childhood cancer, particularly in the long-term. The only previous large-

scale study addressing this topic which did not contribute data to PanCareSurFup is the North American Childhood Cancer Survivor Study (CCSS) [112], which included 108 subsequent primary sarcomas (both bone and soft-tissue combined) compared to our 301 STS alone. More importantly the CCSS study reported just six observed subsequent primary sarcomas beyond 30 years from diagnosis [112], whilst in PanCareSurFup this was 80.

Our study provides, for the first time, separate risk estimates for specific histological types of STS, and shows that childhood cancer survivors are at increased risk of developing a STS SPN, particularly leiomyosarcoma, MPNST and fibromatous SPNs. The differences in SIRs for each STS subtype are more than likely due to differences in the background rate for each of these subtypes in the general population— the incidence of MPNST is lower than fibromatous neoplasm or leiomyosarcoma in the general population, which results in a higher SIR due to MPNST[208]. Among childhood cancer survivors as years from diagnosis and attained age increases the SIR for fibromatous SPNs decreased; in contrast the SIR for leiomyosarcoma and MPNST remained consistently high across all years from diagnosis and at all attained ages. With regards to the AER, the number of excess fibromatous SPNs and MPNST remained low across all years from diagnosis and at all attained ages at less than 1. In contrast the number of excess leiomyosarcomas increased with increasing years from diagnosis and attained age; especially among retinoblastoma survivors. Leiomyosarcoma are associated with the genetic predisposition found in heritable retinoblastoma survivors (RB1 deletion)[209], therefore explains why there is a large excess of this STS subtype among retinoblastoma survivors.

This study observed a 16-fold risk of STS SPNs compared to the general population, which is broadly consistent with the largest studies published so far [96, 100, 104, 112-114], but previous studies were based on far fewer STS events.

To our knowledge our study is the first to identify a substantially increased risk of leiomyosarcoma in Wilms tumour survivors. This increase in risk is likely related to radiotherapy because 10/11 (91%) of leiomyosarcomas observed after Wilms tumour developed within tissue directly irradiated (Table 5.6). The high risk of leiomyosarcoma among retinoblastoma survivors is consistent with previous literature [204, 210, 211] and is most likely caused by a genetic predisposition (heritable retinoblastoma/ RB1 mutation) [205, 211]— 77% of such leiomyosarcomas developed outside of tissue directly irradiated to treat the retinoblastoma and 87% of these retinoblastomas were known to be heritable (Table 5.6). The strong relationship observed between age at childhood cancer and the excess risk of leiomyosarcoma is likely due to a genetic predisposition—65% of survivors diagnosed before age 5 who developed a leiomyosarcoma had a genetic predisposition.

Some of the excess risk of fibromatous SPNs after bone sarcoma and Hodgkin lymphoma can be attributed to radiotherapy as 57% of the fibromatous SPNs observed after bone sarcoma and Hodgkin lymphoma developed within tissue directly irradiated (Table 5.6). Kleinerman *et al* identified an increased risk of both fibrosarcoma (398-fold) and malignant fibrous histiocytoma (100-fold) among survivors of heritable retinoblastoma [205]. The current study included few retinoblastoma survivors (n=6) who developed a fibromatous neoplasm (4 fibrosarcoma, 2 malignant fibrous histiocytoma, 1 dermatofibroma); therefore detailed comparison is not possible.

Neurofibromatosis is a genetic condition associated with the development of cancer, particularly MPNST and CNS tumours (gliomas) [212]. In our cohort, 21/45 (47%) of MPNST were associated with neurofibromatosis, which is consistent with previous reports [213, 214].

Previous literature suggests that MPNSTs may also arise in individuals previously treated with radiotherapy who do not have neurofibromatosis [214]. It is apparent from Table 5.9 that about two-thirds of MPNST developed in tissue directly irradiated to treat the original childhood cancer irrespective of whether neurofibromatosis was known to be present or not.

Over the last few decades (1970s, 1980s, 1990s), cumulative therapeutic exposures have decreased for cancers with a favourable prognosis, however; within PanCareSurFup the excess risk of developing any type of STS did not vary significantly across decades of diagnosis (≤1970, 1970-1979, 1980-1989, 1990-2008). Consequently, there is no evidence so far that interventions to reduce the toxicity of cancer treatments are having measurable impact on the long-term risk of STS SPNs.

The AER for leiomyosarcoma increased substantially with attained age and years from diagnosis after retinoblastoma reaching 53 and 37 excess leiomyosarcomas beyond 45 years from diagnosis and 40 years of age, respectively. This study provides evidence that clinical follow-up guidelines should recommend long-term surveillance for leiomyosarcoma among retinoblastoma survivors. In contrast, the AER for both fibromatous SPNs and MPNSTs remained below 1 across all years from diagnosis and attained ages, i.e. the absolute risk was

low. Thus far there is no evidence to suggest long-term surveillance of fibromatous SPNs or MPNST among childhood cancer survivors is warranted.

5.5.1 Limitations

A potential limitation of our study is the observed significant heterogeneity between the contributing cohorts (Table 5.4). However, when the French cohort was excluded, the p-value for heterogeneity in SIRs between cohorts was no longer significant ($P_{heterogeneity}$=0.083). The French cohort was ascertained through five treatment centres, but a large proportion of survivors attended the two main centres (Institut Gustave Roussy and Insititut Curie) which are international referral centres for difficult cases, particularly with relapsed and recurrent disease. Therefore it was anticipated that cumulative doses of radiotherapy administered to patients at these centres would be higher than in a population-based setting. Sensitivity analyses revealed that SIRs, AERs, RRs and RERs were remarkably similar to those presented here when the French cohort was excluded, therefore we did not exclude French cohort in our analyses (Table 5.12).

A limitation is the absence of detailed information on cumulative radiotherapy and chemotherapy exposure during treatment for the childhood cancer. However a nested case-control study is in progress which will relate the risk of STS SPN to cumulative doses of radiation from radiotherapy and cumulative doses of individual cytotoxic drugs.

5.6 CONCLUSIONS

Childhood cancer survivors are at increased risk of developing STS, particularly leiomyosarcoma, MPNSTs and fibromatous neoplasms. The risk of STS did not vary across

different decades of diagnosis. Whilst the observed risks relative to the general population were substantial, the absolute risk of developing any STS subtype was low, except for leiomyosarcoma after retinoblastoma. These long-term risks provide an evidence base for developing clinical follow-up guidelines.

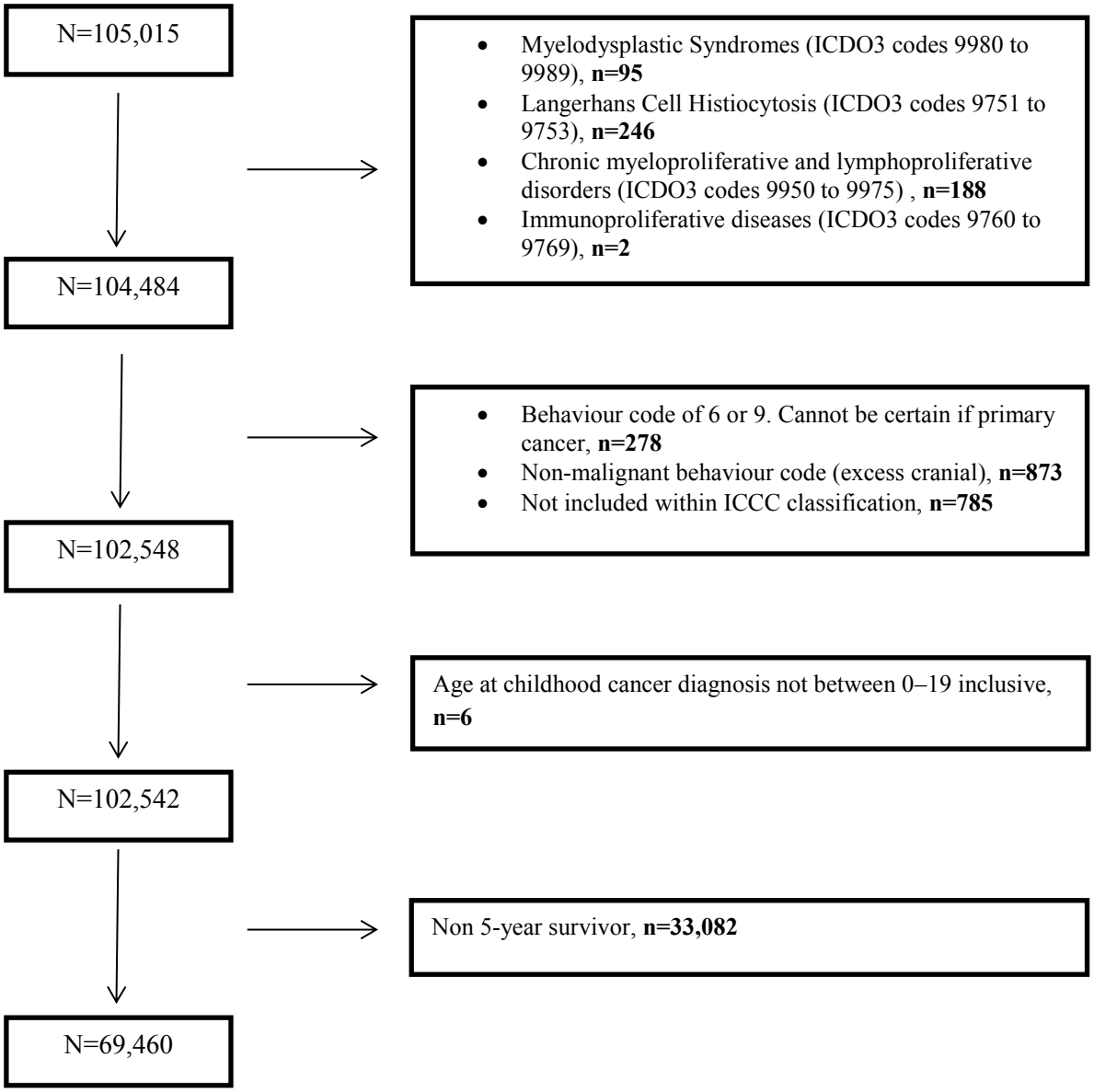


Figure 5.1: Flow diagram showing exclusion criteria for childhood cancer

Table 5.1: Characteristics of 5-year cancer survivor cohorts contributing to the European PanCareSurFup cohort

Cohort	No. of 5-year survivors	Study Design	Period of Childhood Cancer diagnosis	Age at Childhood Cancer Diagnosis	End of Follow-up	Childhood Cancer Inclusion Criteria	Method of SPN Ascertainment	SPN Inclusion Criteria
France	3,138	Treatment centre	1946–1986	<19	Sep-14	malignant or intracranial, excludes leukaemia	Multiple methods[1]	malignant or intracranial
Hungary	4,885	Population based	1971–2008	<20	Dec-14	malignant or intracranial	Multiple methods[2]	malignant or intracranial
Italy PB	7,436	Population based	1965–2005	<20	May-10	malignant or intracranial	Multiple methods[3]	malignant or intracranial
Italy HB	1,490	Treatment centre	1960–2007	<20	Dec-12	malignant or intracranial	Multiple methods[3]	malignant or intracranial
Netherlands	6,044	Population based	1963–2001	<18	Dec-12	malignant or intracranial	Multiple methods[4]	malignant or intracranial
Denmark	4,840	Population based	1943–1998	<20	Dec-03	malignant or intracranial	Population based	malignant, intracranial or of bladder
Sweden	7,709	Population based	1958–1998	<20	Dec-03	malignant or intracranial	Population based	malignant, intracranial or of bladder
Norway	3,783	Population based	1953–1997	<20	Dec-02	malignant or intracranial	Population based	malignant, intracranial or of bladder
Finland	6,229	Population based	1953–2006	<20	Dec-11	malignant or intracranial	Population based	malignant, intracranial or of bladder
Iceland	275	Population based	1955–1998	<20	Dec-03	malignant or intracranial	Population based	malignant, intracranial or of bladder
Slovenia	1,252	Population based	1960–2002	<17	Jul-14	malignant or intracranial	Population based	malignant, intracranial or of bladder
Switzerland	4,379	Population based	1964–2005	<20	Dec-13	malignant or intracranial	Multiple methods[5]	malignant or intracranial
UK	17,960	Population based	1940–1991	<15	Dec-06	malignant or intracranial	Population based	malignant, intracranial or of bladder

Abbreviations: SPN-Subsequent primary neoplasm, PB-population based, HB-hospital based, UK- United Kingdom

[1]Multiple methods include: long-term follow-up clinics, questionnaires to survivors, national mortality records and health insurance registries.

[2]Multiple methods include: long-term follow-up clinics, questionnaires to survivors and medical records/hospital data.

[3]Multiple methods include: medical records/ hospital data, national mortality records.

[4]Multiple methods include: population-based cancer registries, long-term follow-up clinics and medical records/hospital data.

[5]Multiple methods include: population-based cancer registries, long-term follow-up clinics, and national mortality records

Table 5.2: Characteristics of the survivor cohorts included in the PanCareSurFup cohort

	All Countries		France		Hungary		Italy PB		Italy HB		Netherlands		Denmark	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Overall	69,460	100.0	3,138	100.0	4,885	100.0	7,476	100.0	1,490	100.0	6,044	100.0	4,840	100.0
Sex														
Male	37,738	54.3	1,731	55.2	2,729	55.9	4,087	54.7	808	54.2	3,362	55.6	2,684	55.5
Female	31,722	45.7	1,407	44.8	2,156	44.1	3,389	45.3	682	45.8	2,682	44.4	2,156	44.6
Age at Diagnosis														
<5 years	26,969	38.8	1629	51.9	2106	43.1	2,311	30.9	654	43.9	2,733	45.2	1,421	29.4
5–9 years	15,587	22.4	748	23.8	1283	26.3	1,455	19.5	438	29.4	1,627	26.9	859	17.8
10–14 years	15,423	22.2	657	20.9	1135	23.2	1,606	21.5	319	21.4	1,291	21.4	936	19.3
15–19 years	11,482	16.5	104	3.3	361	7.4	2,104	28.1	79	5.3	393	6.5	1,624	33.6
Decade of Diagnosis														
<1970	8,993	13.0	674	21.5	0	0.0	183	2.5	32	2.2	117	1.9	1,214	25.1
1970–1979	13,479	19.4	1,375	43.8	368	7.5	470	6.3	188	12.6	954	15.8	893	18.5
1980–1989	20,900	30.1	1,089	34.7	1,280	26.2	1,404	18.8	338	22.7	1,899	31.4	1,270	26.2
1990–1999	19,260	27.7	0	0.0	1,686	34.5	3,545	47.4	684	45.9	2,487	41.2	1,463	30.2
≥2000	6,828	9.8	0	0.0	1,551	31.8	1,874	25.1	248	16.6	587	9.7	0	0.0
Attained Age														
0–19 years	16,397	23.6	290	9.2	2,190	44.8	2,603	34.8	362	24.3	1,294	21.4	1,081	22.3
20-–29 years	22,329	32.2	445	14.2	1,717	35.2	2,868	38.4	567	38.1	2,078	34.4	1,458	30.1
30–39 years	17,522	25.2	1,050	33.5	798	16.3	1,551	20.8	375	25.2	1,771	29.3	1,099	22.7
≥40 years	13,212	19.0	1,353	43.1	180	3.7	454	6.1	186	12.5	901	14.9	1,202	24.8
Years from Diagnosis														
5–14 years	23,833	34.3	334	10.6	2,752	56.3	4,703	62.9	465	31.2	1,555	25.7	2,018	41.7
15–24 years	22,282	32.1	423	13.5	1,443	29.5	1,871	25.0	576	38.7	2,316	38.3	1,242	25.7
25–34 years	14,087	20.3	1193	38.0	604	12.4	674	9.0	305	20.5	1,583	26.2	748	15.5
35–44 years	6,796	9.8	871	27.8	86	1.8	223	3.0	131	8.8	545	9.0	436	9.0
45+ years	2,462	3.5	317	10.1	0	0.0	5	0.1	13	0.9	45	0.7	396	8.2
FPN Diagnosis														
Leukaemia	16,595	23.9	0	0.0	1,509	30.9	1,805	24.1	671	45.0	2,058	34.1	793	16.4
Hodgkin Lymphoma	6,000	8.6	218	7.0	447	9.2	965	12.9	146	9.8	404	6.7	408	8.4
Non-Hodgkin Lymphoma	3,350	4.8	113	3.6	252	5.2	397	5.3	69	4.6	367	6.1	194	4.0
Central Nervous System	14,096	20.3	442	14.1	964	19.7	1,307	17.5	153	10.3	842	13.9	1,223	25.3
Neuroblastoma	3,169	4.6	419	13.4	361	7.4	314	4.2	102	6.9	319	5.3	123	2.5
Retinoblastoma	2,578	3.7	147	4.7	122	2.5	149	2.0	12	0.8	33	0.6	204	4.2
Wilms Tumour	4,756	6.9	633	20.2	328	6.7	289	3.9	94	6.3	591	9.8	210	4.3
Bone Sarcoma	3,147	4.5	228	7.3	251	5.1	338	4.5	68	4.6	369	6.1	191	4.0
STS	4,502	6.5	362	11.5	246	5.0	417	5.6	76	5.1	451	7.5	339	7.0
Other*	10,905	15.7	576	18.4	405	8.3	1,495	20.0	99	6.6	610	10.1	1,155	23.9
Not classifiable	363	0.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

Table 5.2 continued:

	Sweden		Norway		Finland		Iceland		Slovenia		Switzerland		UK	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Overall	7,709	100.0	3,783	100.0	6,229	100.0	275	100.0	1,252	100.0	4,379	100.0	17,960	100.0
Sex														
Male	4,021	52.2	1,990	52.6	3,180	51.1	152	55.3	692	55.3	2,425	55.4	9,877	55.0
Female	3,688	47.8	1,793	47.4	3,049	49.0	123	44.7	560	44.7	1,954	44.6	8,083	45.0
Age at Diagnosis														
<5 years	2,548	33.1	1,198	31.7	1,982	31.8	77	28.0	451	36.0	1,590	36.3	8,268	46.0
5–9 years	1,407	18.3	622	16.4	1,066	17.1	53	19.3	278	22.2	967	22.1	4,784	26.6
10–14 years	1,433	18.6	650	17.2	1,217	19.5	53	19.3	322	25.7	934	21.3	4,870	27.1
15–19 years	2,321	30.1	1,313	34.7	1,964	31.5	92	33.5	201	16.1	888	20.3	38	0.2
Decade of Diagnosis														
<1970	1,337	17.3	620	16.4	918	14.7	35	12.7	116	9.3	2	0.1	3,745	20.9
1970–1979	1,588	20.6	773	20.4	859	13.8	46	16.7	212	16.9	382	8.7	5,371	29.9
1980–1989	2,263	29.4	1,256	33.2	1,342	21.5	83	30.2	364	29.1	1,170	26.7	7,142	39.8
1990–1999	2,521	32.7	1,134	30.0	1,797	28.9	111	40.4	417	33.3	1,713	39.1	1,702	9.5
≥2000	0	0.0	0	0.0	1,313	21.1	0	0.0	143	11.4	1,112	25.4	0	0.0
Attained Age														
0–19 years	1,955	25.4	917	24.2	1,319	21.2	72	26.2	183	14.6	1,430	32.7	2,701	15.0
20-–29 years	2,311	30.0	1,177	31.1	1,865	29.9	104	37.8	356	28.4	1,906	43.5	5,477	30.5
30–39 years	1,769	23.0	974	25.8	1,426	22.9	48	17.5	364	29.1	758	17.3	5,540	30.9
≥40 years	1,674	21.7	715	18.9	1,619	26.0	51	18.6	349	27.9	285	6.5	4,242	23.6
Years from Diagnosis														
5–14 years	3,188	41.4	1,647	43.5	2,328	37.4	135	49.1	264	21.1	2,384	54.4	2,060	11.5
15–24 years	2,126	27.6	1,130	29.9	1,739	27.9	79	28.7	417	33.3	1,479	33.8	7,441	41.4
25–34 years	1,371	17.8	617	16.3	1,109	17.8	40	14.6	318	25.4	462	10.6	5,063	28.2
35–44 years	954	12.4	311	8.2	609	9.8	19	6.9	185	14.8	54	1.2	2,372	13.2
45+ years	70	0.9	78	2.1	444	7.1	2	0.7	68	5.4	0	0.0	1,024	5.7
FPN Diagnosis														
Leukaemia	1,343	17.4	722	19.1	1,297	20.8	49	17.8	222	17.7	1,275	29.1	4,851	27.0
Hodgkin Lymphoma	660	8.6	297	7.9	616	9.9	30	10.9	99	7.9	384	8.8	1,326	7.4
Non-Hodgkin Lymphoma	235	3.1	127	3.4	401	6.4	6	2.2	61	4.9	248	5.7	880	4.9
Central Nervous System	1,991	25.8	786	20.8	1,333	21.4	57	20.7	168	13.4	721	16.5	4,109	22.9
Neuroblastoma	165	2.1	143	3.8	211	3.4	8	2.9	31	2.5	207	4.7	766	4.3
Retinoblastoma	255	3.3	133	3.5	176	2.8	6	2.2	20	1.6	121	2.8	1,200	6.7
Wilms Tumour	394	5.1	160	4.2	296	4.8	10	3.6	53	4.2	220	5.0	1,478	8.2
Bone Sarcoma	336	4.4	178	4.7	265	4.3	16	5.8	30	2.4	213	4.9	664	3.7
STS	452	5.9	248	6.6	383	6.2	20	7.3	63	5.0	271	6.2	1,173	6.5
Other*	1,878	24.4	989	26.1	1,251	20.1	73	26.6	142	11.3	719	16.4	1,513	8.4
Not classifiable	0	0.0	0	0.0	0	0.0	0	0.0	363	29.0	0	0.0	0	0.0

Abbreviations: FPN- first primary neoplasm; NHL- Non-Hodgkin lymphoma; CNS- Central nervous system; STS- soft tissue sarcoma; PB- population based; HB-hospital based

*Most common 'Other' neoplasms: malignant gonadal germ cell tumours (n=2,285, 21%), malignant melanoma (n=1,439, 13%), thyroid carcinoma (n=1,283, 12%) and Burkitt lymphoma (n-703, 6%).

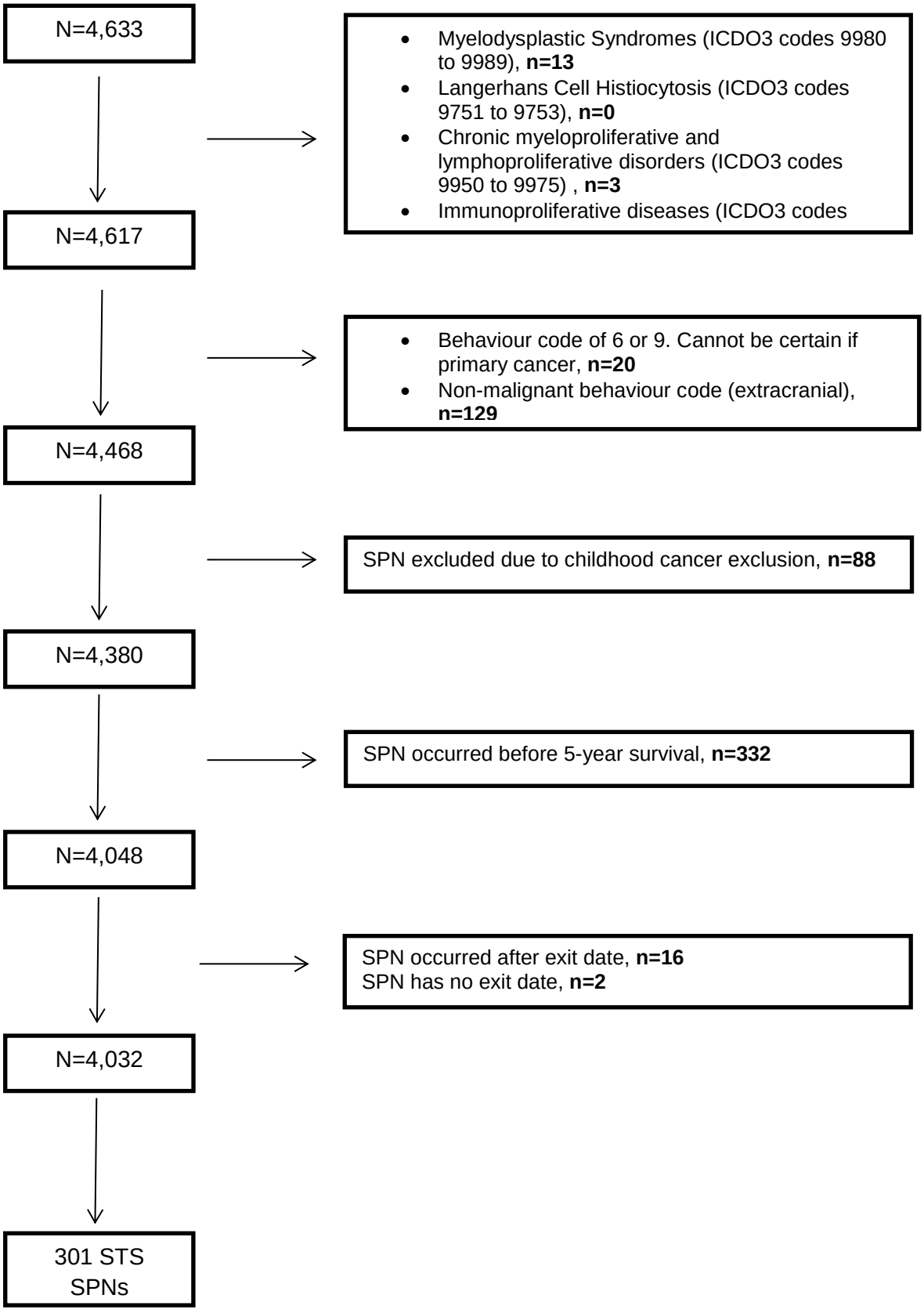


Figure 5.2: Flow diagram showing exclusion criteria for subsequent primary neoplasms

Table 5.3: Standardised incidence ratios (SIRs) and absolute excess risks (AERs) of developing a subsequent primary STS in 69,460 5-year survivors of childhood cancer in the European PanCareSurFup cohort, by histological type.

STS Diagnosis	O/E	SIR (95%CI)	AER (95%CI)
All STS	301/19.2	15.7 (14.0 to 17.6)	2.5 (2.2 to 2.8)
Malignant Peripheral Nerve Sheath Tumour	45/1.1	40.6 (29.6 to 54.3)	0.4 (0.3 to 0.5)
Leiomyosarcoma	80/2.7	29.9 (23.7 to 37.2)	0.7 (0.5 to 0.8)
Fibromatous Neoplasms	55/4.5	12.3 (9.3 to 16.0)	0.4 (0.3 to 0.6)
Malignant Fibrous Histiocytoma	25/0.9	28.3 (18.3 to 41.7)	0.2 (0.1 to 0.3)
Fibrosarcoma	27/1.1	25.1 (16.5 to 36.5)	0.2 (0.1 to 0.3)
Dermatofibroma	3/2.5	1.2 (0.2 to 3.5)	0.0 (-0.0 to 0.0)
Rhabdomyosarcoma	22/1.6	13.4 (8.4 to 20.4)	0.2 (0.1 to 0.3)
Liposarcoma	19/1.8	10.5 (6.3 to 16.4)	0.2 (0.1 to 0.2)
Synovial Sarcoma	9/1.3	6.8 (3.1 to 12.9)	0.1 (0.0 to 0.1)
Other Specified Sarcoma	4/0.6	6.3 (1.7 to 16.2)	0.0 (-0.0 to 0.1)
Blood Vessel Tumour	12/2.5	4.8 (2.5 to 8.3)	0.1 (0.0 to 0.1)
Clear Cell Sarcoma	0/0.1	-	-
Alveolar Soft Part Sarcoma	0/0.1	-	-
Unspecified Sarcoma	55/2.6	20.9 (15.8 to 27.3)	0.5 (0.3 to 0.6)

Abbreviations: O– observed number of STS, E – expected number of STS, SIR- standardised incidence ratio, AER- absolute excess risk, 95%CI- 95% confidence interval.

Table 5.4: Risk of developing a subsequent primary STS among 69,460 5-year survivors of childhood cancer by potential explanatory factors.

Factor	Level	O/E	SIR (95% CI)	RR (95% CI)*	AER (95% CI)	RER (95% CI)*
Overall	All combined	301/19.2	15.7 (14.0 to 17.6)		2.5 (2.2 to 2.8)	
Sex	Male	161/10.5	15.4 (13.1 to 17.9)	*Ref*	2.5 (2.1 to 2.9)	*Ref*
	Female	140/8.7	16.1 (13.6 to 19.0)	1.2 (0.9–1.5)	2.5 (2.1 to 2.9)	1.0 (0.8–1.3)
	$P_{heterogeneity}$		*0.648*	*0.235*	*0.992*	*0.922*
Country	France	48/1.5	32.2 (23.8 to 42.7)	*Ref*	5.6 (4.0 to 7.2)	*Ref*
	Hungary	6/0.6	9.6 (3.5 to 20.9)	0.3 (0.1 to 0.8)	1.1 (0.1 to 2.0)	0.3 (0.1 to 0.8)
	Italy (PB)	12/1.0	11.8 (6.1 to 20.5)	0.4 (0.2 to 0.8)	1.6 (0.6 to 2.5)	0.4 (0.2 to 0.8)
	Italy (HB)	1/0.3	3.0 (0.1 to 16.6)	0.1 (0.0 to 0.9)	0.3 (-0.6 to 1.1)	0.1 (0.0 to 1.1)
	Netherlands	32/1.5	20.8 (14.2 to 29.4)	0.8 (0.5 to 1.3)	2.9 (1.9 to 4.0)	0.8 (0.5 to 1.3)
	Denmark	18/1.7	10.3 (6.1 to 16.3)	0.4 (0.2 to 0.7)	2.1 (1.0 to 3.1)	0.4 (0.2 to 0.7)
	Sweden	25/2.2	11.4 (7.4 to 16.8)	0.4 (0.3 to 0.7)	2.0 (1.1 to 2.8)	0.4 (0.3 to 0.8)
	Norway	9/1.0	9.0 (4.1 to 17.2)	0.3 (0.2 to 0.7)	1.5 (0.4 to 2.6)	0.4 (0.2 to 0.8)
	Finland	27/2.3	12.0 (7.9 to 17.4)	0.5 (0.3 to 0.8)	2.4 (1.4 to 3.3)	0.5 (0.3 to 0.8)
	Iceland	2/0.1	30.6 (3.7 to 110.7)	1.2 (0.3 to 5.1)	5.6 (-2.4 to 13.6)	1.3 (0.3 to 5.9)
	Slovenia	5/0.5	10.9 (3.6 to 25.5)	0.7 (0.2 to 2.0)	1.8 (0.1 to 3.6)	0.7 (0.2 to 2.2)
	Switzerland	9/0.6	14.5 (6.6 to 27.5)	0.5 (0.2 to 1.1)	1.8 (0.5 to 3.1)	0.5 (0.2 to 1.1)
	UK	107/5.8	18.4 (15.1 to 22.3)	0.5 (0.4 to 0.8)	2.7 (2.2 to 3.3)	0.5 (0.4 to 0.8)
	$P_{heterogeneity}$		*<0.001*	*<0.001*	*<0.001*	*0.003*
Age at Diagnosis	0–4 years	142/5.9	24.2 (20.3 to 28.5)	*Ref*	2.9 (2.4 to 3.4)	*Ref*
	5–9 years	50/4.0	12.4 (9.2 to 16.3)	0.9 (0.6 to 1.3)	1.8 (1.3 to 2.3)	0.9 (0.6 to 1.3)
	10–14 years	73/5.2	14.1 (11.0 to 17.7)	1.1 (0.7 to 1.6)	2.7 (2.0 to 3.4)	1.1 (0.7 to 1.7)
	15–19years	36/4.1	8.9 (6.2 to 12.3)	0.9 (0.5 to 1.5)	2.1 (1.3 to 2.8)	0.8 (0.5 to 1.5)
	P_{trend}		*<0.001*	*0.951*	*0.150*	*0.937*
Type of first Childhood Cancer	Leukaemia	19/2.8	6.8 (4.1 to 10.6)	*Ref*	0.7 (0.3 to 1.1)	*Ref*
	Hodgkin Lymphoma	33/1.7	19.0 (13.1 to 26.7)	3.2 (1.8 to 5.8)	3.6 (2.3 to 4.9)	3.5 (1.8 to 6.8)
	Non-Hodgkin Lymphoma	8/1.0	8.1 (3.5 to 16.0)	1.3 (0.6 to 3.0)	1.3 (0.3 to 2.3)	1.3 (0.5 to 3.4)
	Central Nervous System	42/4.0	10.4 (7.5 to 14.0)	1.7 (1.0 to 3.0)	1.7 (1.1 to 2.2)	1.8 (1.0 to 3.4)
	Neuroblastoma	17/0.7	24.5 (14.3 to 39.2)	3.0 (1.5 to 5.8)	3.0 (1.5 to 4.4)	3.2 (1.5 to 6.7)
	Retinoblastoma	64/0.9	72.8 (56.1 to 93.0)	10.9 (6.3 to 19.0)	10.5 (7.9 to 13.1)	12.2 (6.6 to 22.7)
	Wilms Tumour	34/1.3	25.5 (17.6 to 35.6)	3.2 (1.8 to 5.7)	3.4 (2.2 to 4.6)	3.5 (1.8 to 6.7)
	Bone Sarcoma	23/1.1	21.1 (13.4 to 31.6)	3.3 (1.8 to 6.4)	4.2 (2.4 to 6.0)	3.7 (1.8 to 7.5)
	STS	26/1.5	17.1 (11.2 to 25.1)	2.6 (1.4 to 4.8)	3.0 (1.8 to 4.2)	2.9 (1.5 to 5.7)
	Other	34/3.8	9.0 (6.2 to 12.5)	1.6 (0.9 to 2.9)	1.7 (1.0 to 2.3)	1.7 (0.9 to 3.3)
	Not classifiable[†]	1/0.3	3.7 (0.1 to 20.8)	-	0.6 (-1.0 to 2.3)	-
	$P_{heterogeneity}$		*<0.001*	*<0.001*	*<0.001*	*<0.001*
Decade of Diagnosis	<1970	114/6.9	16.6 (13.7 to 19.9)	1.2 (0.9 to 1.6)	3.7 (3.0 to 4.5)	1.1 (0.8 to 1.5)
	1970-1979	84/5.4	15.4 (12.3 to 19.1)	*Ref*	2.5 (1.9 to 3.1)	*Ref*
	1980-1989	67/4.7	14.1 (11.0 to 18.0)	0.9 (0.7 to 1.3)	1.8 (1.4 to 2.3)	1.0 (0.7 to 1.4)
	>=1990	36/2.1	17.2 (12.1 to 23.9)	1.3 (0.8 to 2.0)	1.8 (1.2 to 2.4)	1.4 (0.8 to 2.2)
	P_{trend}		*0.632*	*0.699*	*<0.001*	*0.842*
Attained Age	0–19 years	69/3.2	21.2 (16.5 to 26.9)	*Ref*	1.6 (1.2 to 2.0)	*Ref*
	20–29 years	95/5.6	16.9 (13.6 to 20.6)	0.8 (0.6 to 1.2)	2.3 (1.8 to 2.8)	1.6 (1.1 to 2.2)
	30–39 years	83/5.3	15.8 (12.6 to 19.6)	0.7 (0.5 to 1.1)	3.6 (2.8 to 4.5)	2.5 (1.7 to 3.6)
	40+ years	54/5.0	10.8 (8.1 to 14.0)	0.5 (0.3 to 0.8)	4.3 (3.0 to 5.5)	2.9 (1.8 to 4.5)
	P_{trend}		*<0.001*	*0.002*	*<0.001*	*<0.001*
Years from Diagnosis	5–14 years	108/5.7	18.8 (15.4 to 22.7)	*Ref*	1.8 (1.4 to 2.2)	*Ref*
	15–24 years	82/5.8	14.2 (11.3 to 17.6)	0.7 (0.5 to 0.9)	2.3 (1.7 to 2.8)	1.2 (0.9 to 1.6)
	25–34 years	58/4.5	13.0 (9.8 to 16.7)	0.5 (0.4 to 0.7)	3.4 (2.4 to 4.3)	1.6 (1.1 to 2.3)
	35–44 years	41/2.3	17.5 (12.6 to 23.8)	0.6 (0.4 to 0.9)	7.1 (4.8 to 9.4)	3.1 (2.0 to 4.8)
	45+ years	12/0.8	15.0 (7.8 to 26.2)	0.5 (0.2 to 0.9)	9.1 (3.6 to 14.6)	3.7 (1.9 to 7.2)
	P_{trend}		*0.298*	*0.001*	*<0.001*	*<0.001*

Abbreviations: O– observed number of STS, E – expected number of STS, SIR- standardised incidence ratio, AER- absolute excess risk, 95%CI- 95% confidence interval, PB- population based, HB- hospital based, RR- relative risk, RER- relative excess risk, ref- reference category

[†]Childhood cancer survivors diagnosed in Slovenia before 1983 – excluded from multivariable analysis

* Model containing years from diagnosis was adjusted for gender, country, age at diagnosis, childhood cancer diagnosis and decade of childhood cancer diagnosis. Model containing attained age was adjusted for gender, country, age at diagnosis, childhood cancer diagnosis and decade of childhood cancer diagnosis. Not classifiable tumours were excluded from multivariable analysis.

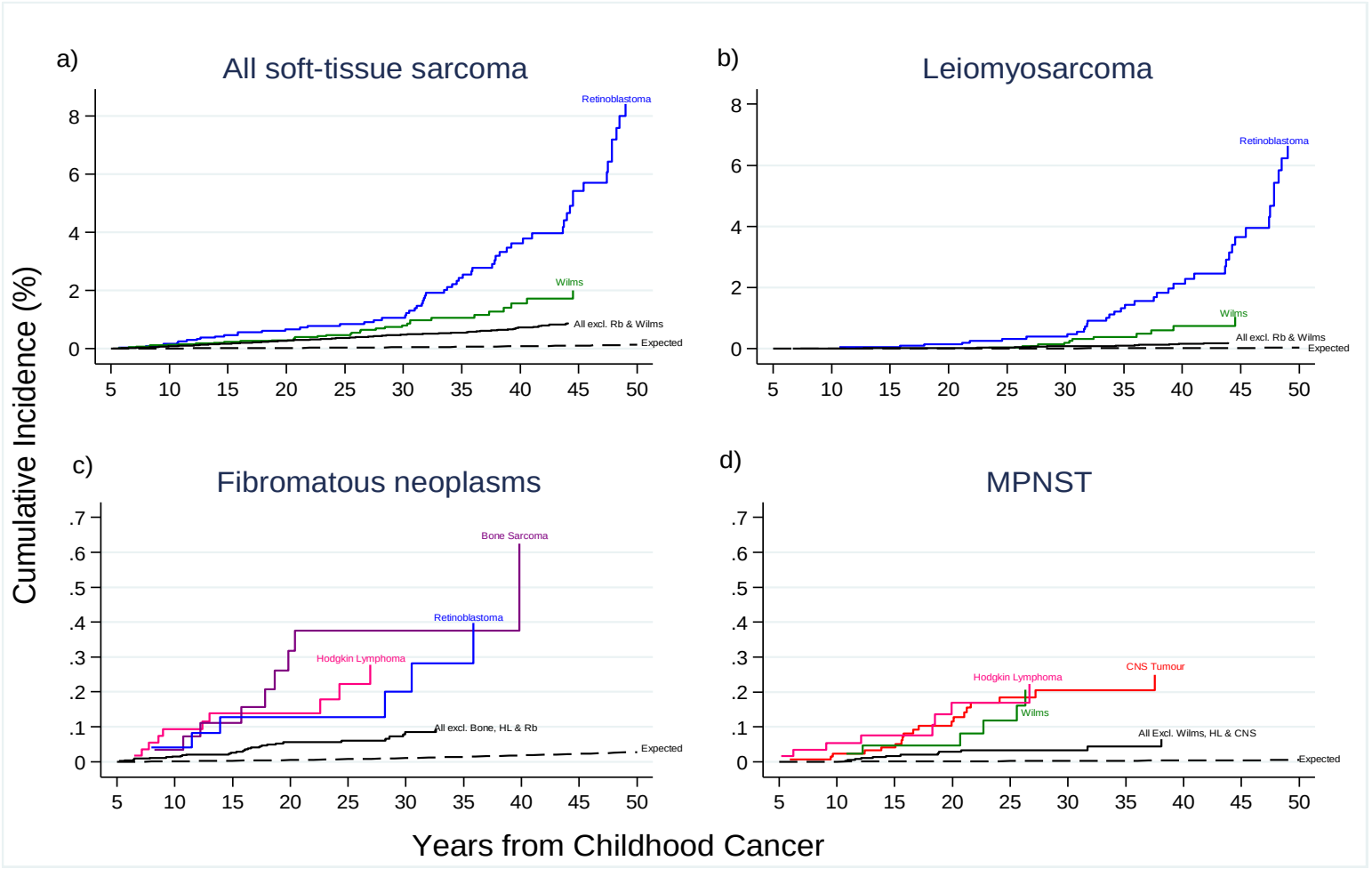


Figure 5.3: Cumulative incidence of all and selected histological types of subsequent primary STS in 5-year survivors of childhood cancer, by years from diagnosis.

Abbreviations: HL- Hodgkin lymphoma; CNS- central nervous system; Rb-retinoblastoma; STS- soft tissue sarcoma; MPNST– malignant peripheral nerve sheath tumours

Table 5.5: Risk of subsequent primary leiomyosarcoma among 69,460 5-year survivors of childhood cancer, by potential explanatory factors

Factor	Level	O/E	SIR (95% CI)	RR (95% CI)*	AER (95% CI)	RER (95%CI)*
Overall	All combined	80/2.7	29.9 (23.7 to 37.2)		0.7 (0.5 to 0.8)	
Sex	Male	32/0.9	36.6 (25.0 to 51.7)	*Ref*	0.5 (0.3 to 0.7)	*Ref*
	Female	48/1.8	26.6 (19.6 to 35.3)	0.9 (0.6–1.5)	0.9 (0.6 to 1.1)	1.7 (1.1–2.7)
	$P_{heterogeneity}$		*0.159*	*0.762*	*0.021*	*0.029*
Country	France	17/0.2	84.0 (48.9 to 134.5)	*Ref*	2.0 (1.0 to 3.0)	*Ref*
	Hungary	1/0.0	21.7 (0.5 to 120.7)	0.3 (0.0 to 2.4)	0.2 (-0.2 to 0.6)	0.3 (0.0 to 2.2)
	Italy[1]	1/0.1	8.0 (0.2 to 44.4)	0.1 (0.0 to 1.1)	0.1 (-0.1 to 0.3)	0.1 (0.0 to 1.3)
	Netherlands	4/0.1	27.5 (7.5 to 70.3)	0.5 (0.2 to 1.5)	0.4 (-0.0 to 0.8)	0.5 (0.1 to 1.5)
	Nordic Countries[2]	13/1.3	10.3 (5.5 to 17.7)	0.2 (0.1 to 0.5)	0.3 (0.1 to 0.5)	0.2 (0.1 to 0.5)
	Slovenia	0/0.1	-	-	-	-
	Switzerland	0/0.1	-	-	-	-
	UK	44/0.8	56.0 (40.7 to 75.1)	0.5 (0.3 to 1.0)	1.2 (0.8 to 1.5)	0.5 (0.3 to 1.0)
	$P_{heterogeneity}$		*<0.001*	*0.002*	*<0.001*	*0.002*
Age at Diagnosis	0–4 years	57/0.6	98.3 (74.4 to 127.4)	*Ref*	1.2 (0.9 to 1.5)	*Ref*
	5–9 years	10/0.5	20.7 (9.9 to 38.1)	0.6 (0.3 to 1.3)	0.4 (0.1 to 0.6)	0.6 (0.3 to 1.5)
	10–19 years	13/1.6	8.0 (4.3 to 13.8)	0.3 (0.1 to 0.8)	0.3 (0.1 to 0.5)	0.4 (0.1 to 1.0)
	P_{trend}		*<0.001*	*0.011*	*<0.001*	*0.042*
Type of Childhood Cancer	Leukaemia	2/0.2	8.2 (1.0 to 29.5)	*Ref*	0.1 (-0.0 to 0.2)	*Ref*
	Hodgkin Lymphoma	4/0.2	17.2 (4.7 to 44.0)	4.0 (0.7 to 23.3)	0.4 (-0.0 to 0.9)	4.1 (0.6 to 26.2)
	Non-Hodgkin Lymphoma	1/0.1	8.2 (0.2 to 45.7)	1.4 (0.1 to 16.2)	0.2 (-0.2 to 0.5)	1.3 (0.1 to 20.6)
	Central Nervous System	1/0.6	1.7 (0.0 to 9.4)	0.3 (0.0 to 3.7)	0.0 (-0.1 to 0.1)	0.2 (0.0 to 11.7)
	Neuroblastoma	2/0.1	28.8 (3.5 to 103.9)	2.0 (0.3 to 15.0)	0.3 (-0.2 to 0.9)	1.8 (0.2 to 14.7)
	Retinoblastoma	40/0.1	342.9 (245.0 to 466.9)	30.2 (6.8 to 134.9)	6.6 (4.6 to 8.7)	31.2 (6.6 to 146.9)
	Wilms Tumour	11/0.1	74.2 (37.1 to 132.8)	5.3 (1.1 to 25.4)	1.1 (0.5 to 1.8)	5.3 (1.0 to 26.7)
	Bone Sarcoma	5/0.2	28.9 (9.4 to 67.4)	6.6 (1.2 to 36.8)	0.9 (0.1 to 1.8)	6.8 (1.1 to 40.9)
	STS	6/0.2	26.4 (9.7 to 57.4)	4.3 (0.8 to 22.4)	0.7 (0.1 to 1.3)	4.4 (0.8 to 24.1)
	Other	8/0.7	11.3 (4.9 to 22.4)	3.2 (0.6 to 16.3)	0.4 (0.1 to 0.7)	3.3 (0.6 to 17.9)
	Not classifiable[†]	0/0.0	-	-	-	-
	$P_{heterogeneity}$		*<0.001*	*<0.001*	*<0.001*	*<0.001*
Decade of Diagnosis	<1970	48/1.4	33.3 (24.6 to 44.2)	1.0 (0.5 to 2.0)	1.6 (1.1 to 2.1)	1.1 (0.6 to 2.1)
	1970–1979	17/0.7	25.0 (14.6 to 40.0)	*Ref*	0.5 (0.3 to 0.8)	*Ref*
	>=1980	15/0.6	26.8 (15.0 to 44.3)	1.8 (0.9 to 3.8)	0.3 (0.1 to 0.4)	1.5 (0.7 to 3.3)
	P_{trend}		*0.347*	*0.235*	*<0.001*	*0.502*
Attained Age	0–29 years	22/0.6	35.4 (22.2 to 53.7)	*Ref*	0.3 (0.2 to 0.4)	*Ref*
	30–39 years	26/0.7	37.0 (24.2 to 54.3)	1.1 (0.6 to 2.1)	1.2 (0.7 to 1.6)	5.4 (2.9 to 10.1)
	40+ years	32/1.4	23.6 (16.1 to 33.3)	0.9 (0.4 to 1.9)	2.7 (1.7 to 3.7)	12.5 (6.3 to 25.0)
	P_{trend}		*0.128*	*0.765*	*<0.001*	*<0.001*
Years from Diagnosis	5–24 years	18/1.0	17.5 (10.4 to 27.6)	*Ref*	0.2 (0.1 to 0.3)	*Ref*
	25–34 years	28/0.8	33.7 (22.4 to 48.6)	1.9 (0.9 to 3.7)	1.7 (1.1 to 2.4)	8.0 (4.0 to 16.1)
	35–44 years	23/0.6	38.3 (24.3 to 57.5)	1.7 (0.7 to 3.8)	4.1 (2.4 to 5.8)	17.0 (7.5 to 38.6)
	45+ years	11/0.2	50.7 (25.3 to 90.7)	1.3 (0.5 to 3.3)	8.7 (3.5 to 14.0)	28.2 (11.0 to 72.1)
	P_{trend}		*0.001*	*0.520*	*<0.001*	*<0.001*

Abbreviations: O– observed number of leiomyosarcoma, E – expected number of leiomyosarcoma, SIR- standardised incidence ratio, AER- absolute excess risk, 95%CI- 95% confidence interval, PB- population based, HB- hospital based, RR- relative risk, RER- relative excess risk, ref- reference category

[1]Due to small numbers all Italian cohorts were grouped

[2]Due to small numbers all Nordic cohorts were grouped

[†]Childhood cancer survivors diagnosed in Slovenia before 1983– excluded from multivariable analysis

* Model containing years from diagnosis was adjusted for gender, country, age at diagnosis, childhood cancer diagnosis and decade of childhood cancer diagnosis. Model containing attained age was adjusted for gender, country, age at diagnosis, childhood cancer diagnosis and decade of childhood cancer diagnosis. Not classifiable tumours were excluded from multivariable analysis.

Table 5.6: Location of STS with regards to radiotherapy field (inside/outside) for original childhood cancer.

LEIOMYOSARCOMA			
Childhood Cancer	**Inside RT Field**	**Outside RT Field[$]**	**Unknown**
Leukaemia	1 (50%)	1 (50%)	0
Hodgkin Lymphoma	2 (100%)	0	2
Non-Hodgkin Lymphoma	0	0	1
Central Nervous System	0	1 (100%)	0
Neuroblastoma	2 (100%)	0	0
Retinoblastoma	9 (23%)[*]	30 (77%)[#]	1
Wilms tumour	10 (91%)	1 (9%)	0
Bone tumour	1 (20%)	4 (80%)	0
Soft-tissue sarcoma	3 (50%)	3 (50%)	0
Other	5 (71%)	2 (29%)	1
Total	33 (44%)	42 (56%)	5
FIBROMATOUS NEOPLASMS			
Childhood Cancer	**Inside RT Field**	**Outside RT Field**	**Unknown**
Leukaemia	2 (67%)	1 (33%)	0
Hodgkin Lymphoma	4 (57%)	3 (43%)	3
Non-Hodgkin Lymphoma	0	1 (100%)	0
Central Nervous System	3 (38%)	5 (63%)	0
Neuroblastoma	1 (100%)	0	0
Retinoblastoma	5 (83%)	1 (17%)	0
Wilms tumour	4 (100%)	0	0
Bone tumour	4 (57%)	3 (43%)	2
Soft-tissue sarcoma	4 (67%)	2 (33%)	2
Other	1 (50%)	1 (50%)	3
Total	28 (62%)	17 (38%)	10
MALIGNANT PERIPHERAL NERVE SHEATH TUMOURS			
Childhood Cancer	**Inside RT Field**	**Outside RT Field**	**Unknown**
Leukaemia	1 (33%)	2 (67%)	0
Hodgkin Lymphoma	6 (86%)	1 (14%)	1
Non-Hodgkin Lymphoma	1 (50%)	1 (50%)	0
Central Nervous System	6 (38%)	10 (63%)	3
Neuroblastoma	2 (100%)	0	0
Retinoblastoma	0	0	0
Wilms tumour	5 (83%)	1 (17%)	0
Bone tumour	0	0	0
Soft-tissue sarcoma	3 (100%)	0	0
Other	2 (100%)	0	0
Total	26 (63%)	15 (37%)	4

Percentages calculated for those that have information on whether STS is located within the field or not.

[$] Includes those not receiving radiotherapy for the original childhood cancer

* 8 (89%) of these 9 retinoblastomas were heritable

[#] 26 (87%) of these 30 retinoblastomas were heritable.

Table 5.7: Risk of subsequent primary fibromatous neoplasms among 69,460 5-year survivors of childhood cancer survivors, by potential explanatory factors

Factor	Level	O/E	SIR (95% CI)	RR (95% CI)*	AER (95% CI)	RER (95% CI)*
Overall	All combined	55/4.5	12.3 (9.3 to 16.0)		0.4 (0.3 to 0.6)	
Sex	Male	36/2.3	15.7 (11.0 to 21.8)	*Ref*	0.6 (0.4 to 0.8)	*Ref*
	Female	19/2.2	8.7 (5.2 to 13.6)	0.6 (0.3–1.0)	0.3 (0.2 to 0.5)	0.6 (0.3–1.2)
	$P_{heterogeneity}$		*0.034*	*0.056*	*0.079*	*0.138*
Country	France	12/0.3	43.0 (22.2 to 75.2)	*Ref*	1.4 (0.6 to 2.2)	*Ref*
	Hungary	2/0.1	16.7 (2.0 to 60.5)	0.3 (0.1 to 1.4)	0.4 (-0.2 to 0.9)	0.3 (0.1 to 1.5)
	Italy[1]	3/0.3	11.2 (2.3 to 32.9)	0.2 (0.1 to 0.8)	0.3 (-0.1 to 0.7)	0.2 (0.0 to 0.9)
	Netherlands	5/0.3	16.9 (5.5 to 39.4)	0.4 (0.1 to 1.1)	0.5 (0.0 to 0.9)	0.4 (0.1 to 1.2)
	Nordic Countries[2]	19/2.2	8.6 (5.2 to 13.5)	0.2 (0.1 to 0.4)	0.5 (0.2 to 0.7)	0.3 (0.1 to 0.7)
	Slovenia	1/0.1	11.5 (0.3 to 64.0)	0.5 (0.1 to 4.3)	0.4 (-0.4 to 1.2)	0.4 (0.0 to 6.8)
	Switzerland	1/0.1	8.5 (0.2 to 47.3)	0.2 (0.0 to 1.3)	0.2 (-0.2 to 0.6)	0.1 (0.0 to 1.7)
	UK	12/1.1	10.8 (5.6 to 18.9)	0.2 (0.1 to 0.5)	0.3 (0.1 to 0.5)	0.2 (0.1 to 0.5)
	$P_{heterogeneity}$		*0.001*	*0.016*	*0.047*	*0.065*
Age at Diagnosis	0–4 years	16/1.2	12.9 (7.3 to 20.9)	*Ref*	0.3 (0.1 to 0.5)	*Ref*
	5–9 years	13/0.9	14.6 (7.8 to 25.0)	1.6 (0.7 to 3.8)	0.5 (0.2 to 0.8)	2.0 (0.8 to 5.1)
	10–14 years	15/1.2	12.6 (7.0 to 20.7)	1.8 (0.7 to 4.5)	0.5 (0.2 to 0.9)	2.3 (0.8 to 6.6)
	15–19years	11/1.1	9.6 (4.8 to 17.1)	2.4 (0.8 to 7.1)	0.6 (0.2 to 1.1)	3.1 (0.9 to 11.3)
	P_{trend}		*0.437*	*0.199*	*0.067*	*0.09*
Type of Childhood Cancer	Leukaemia	3/0.6	5.0 (1.0 to 14.5)	*Ref*	0.1 (-0.0 to 0.3)	*Ref*
	Hodgkin Lymphoma	10/0.4	24.2 (11.6 to 44.4)	5.1 (1.3 to 20.0)	1.1 (0.4 to 1.8)	7.0 (1.1 to 43.3)
	Non-Hodgkin Lymphoma	1/0.2	4.5 (0.1 to 25.2)	0.9 (0.1 to 8.7)	0.1 (-0.2 to 0.5)	1.2 (0.1 to 17.9)
	Central Nervous System	8/1.0	8.2 (3.5 to 16.2)	1.9 (0.5 to 7.3)	0.3 (0.1 to 0.6)	2.3 (0.3 to 14.7)
	Neuroblastoma	1/0.1	7.1 (0.2 to 39.3)	1.1 (0.1 to 11.1)	0.2 (-0.2 to 0.5)	1.5 (0.1 to 21.7)
	Retinoblastoma	6/0.2	31.0 (11.4 to 67.5)	8.0 (1.8 to 35.3)	1.0 (0.2 to 1.8)	11.5 (1.6 to 83.9)
	Wilms Tumour	4/0.3	14.2 (3.9 to 36.4)	2.3 (0.5 to 10.9)	0.4 (-0.0 to 0.8)	3.2 (0.4 to 24.2)
	Bone Sarcoma	9/0.3	34.5 (15.8 to 65.5)	6.9 (1.7 to 27.6)	1.7 (0.6 to 2.8)	9.6 (1.5 to 61.0)
	STS	8/0.4	22.6 (9.8 to 44.5)	4.5 (1.2 to 17.9)	0.9 (0.3 to 1.6)	6.4 (1.0 to 41.1)
	Other	5/1.0	5.1 (1.7 to 11.9)	1.3 (0.3 to 5.6)	0.2 (-0.0 to 0.5)	1.4 (0.2 to 11.1)
	Not classifiable[†]	0/0.0	-	-	-	-
	$P_{heterogeneity}$		*<0.001*	*0.001*	*<0.001*	*0.001*
Decade of Diagnosis	<1970	19/1.7	11.3 (6.8 to 17.7)	1.4 (0.7 to 2.8)	0.6 (0.3 to 0.9)	1.2 (0.6 to 2.5)
	1970–1979	16/1.3	12.5 (7.2 to 20.4)	*Ref*	0.5 (0.2 to 0.7)	*Ref*
	1980–1989	11/1.1	10.2 (5.1 to 18.3)	0.7 (0.3 to 1.6)	0.3 (0.1 to 0.5)	0.6 (0.3 to 1.5)
	>=1990	9/0.4	20.3 (9.3 to 38.5)	1.3 (0.5 to 3.4)	0.5 (0.1 to 0.8)	1.1 (0.4 to 3.2)
	P_{trend}		*0.397*	*0.314*	*0.184*	*0.387*
Attained Age	0–19 years	18/0.5	33.5 (19.9 to 53.0)	*Ref*	0.4 (0.2 to 0.6)	*Ref*
	20–29 years	18/1.5	11.8 (7.0 to 18.6)	0.2 (0.1 to 0.5)	0.4 (0.2 to 0.6)	0.6 (0.3 to 1.4)
	30+ years	19/2.4	7.9 (4.8 to 12.3)	0.1 (0.1 to 0.3)	0.5 (0.2 to 0.8)	0.5 (0.2 to 1.3)
	P_{trend}		*<0.001*	<0.001	*0.655*	0.169
Years from Diagnosis	5–14 years	26/1.3	19.7 (12.9 to 28.9)	*Ref*	0.4 (0.3 to 0.6)	*Ref*
	15–24 years	19/1.5	12.8 (7.7 to 19.9)	0.5 (0.3 to 1.0)	0.5 (0.3 to 0.8)	1.1 (0.5 to 2.1)
	25+ years	10/1.7	6.0 (2.9 to 11.0)	0.2 (0.1 to 0.4)	0.4 (0.1 to 0.6)	0.5 (0.2 to 1.4)
	P_{trend}		*0.001*	*<0.001*	*0.879*	*0.11*

Abbreviations: O– observed number of STS, E – expected number of STS, SIR- standardised incidence ratio, AER- absolute excess risk, 95%CI- 95% confidence interval, RR – relative risk, RER – relative excess risk, ref – reference category

[1]Due to small numbers all Italian cohorts were grouped

[2]Due to small numbers all Nordic cohorts were grouped

[3]Due to small numbers bone sarcomas and STS were grouped

[†]Childhood cancer survivors diagnosed in Slovenia before 1983 – excluded from multivariable analysis

* Model containing follow-up is adjusted for gender, country, age at diagnosis, childhood cancer diagnosis and decade of childhood cancer diagnosis. Model containing attained age is adjusted for gender, country, age at diagnosis, childhood cancer diagnosis and decade of childhood cancer diagnosis. Not classifiable tumours were excluded from multivariable analysis.

Table 5.8: Risk of subsequent primary malignant peripheral nerve sheath tumours among 69,460 5-year survivors of childhood cancer survivors, by potential explanatory factors

Factor	Level	O/E	SIR (95% CI)	RR (95% CI)*	AER (95% CI)	RER (95% CI)*
Overall	All combined	45/1.1	40.6 (29.6 to 54.3)		0.4 (0.3 to 0.5)	
Sex	Male	26/0.6	42.1 (27.5 to 61.8)	*Ref*	0.4 (0.3 to 0.6)	*Ref*
	Female	19/0.5	38.6 (23.2 to 60.3)	1.0 (0.5–1.8)	0.4 (0.2 to 0.5)	0.9 (0.5–1.6)
	$P_{heterogeneity}$		*0.77*	*0.995*	*0.56*	*0.686*
Country	France	6/0.1	93.1 (34.2 to 202.7)	*Ref*	0.7 (0.1 to 1.3)	*Ref*
	Hungary	2/0.0	50.2 (6.1 to 181.5)	0.5 (0.1 to 2.7)	0.4 (-0.2 to 0.9)	0.5 (0.1 to 3.0)
	Italy[1]	3/0.1	37.6 (7.8 to 109.8)	0.4 (0.1 to 1.9)	0.3 (-0.1 to 0.7)	0.5 (0.1 to 2.1)
	Netherlands	3/0.1	35.1 (7.2 to 102.7)	0.4 (0.1 to 1.8)	0.3 (-0.0 to 0.6)	0.5 (0.1 to 2.0)
	Nordic Countries[2]	14/0.5	29.3 (16.0 to 49.2)	0.3 (0.1 to 0.9)	0.4 (0.2 to 0.6)	0.5 (0.2 to 1.6)
	Slovenia	0/0.0	-	-	-	-
	Switzerland	3/0.0	78.9 (16.3 to 230.7)	0.9 (0.2 to 4.0)	0.6 (-0.1 to 1.4)	1.0 (0.2 to 4.6)
	UK	14/0.3	46.3 (25.3 to 77.7)	0.5 (0.2 to 1.3)	0.4 (0.2 to 0.6)	0.5 (0.2 to 1.5)
	$P_{heterogeneity}$		*0.328*	*0.526*	*0.796*	*0.828*
Age at Diagnosis	0–4 years	19/0.4	51.1 (30.7 to 79.8)	*Ref*	0.4 (0.2 to 0.6)	*Ref*
	5–9 years	4/0.2	16.2 (4.4 to 41.4)	0.2 (0.1 to 0.7)	0.1 (-0.0 to 0.3)	0.2 (0.1 to 0.8)
	10–14 years	15/0.3	54.1 (30.3 to 89.2)	0.8 (0.3 to 1.8)	0.6 (0.3 to 0.9)	0.8 (0.3 to 1.9)
	15–19years	7/0.2	33.0 (13.3 to 67.9)	0.7 (0.2 to 2.3)	0.4 (0.1 to 0.8)	0.7 (0.2 to 2.3)
	P_{trend}		*0.657*	*0.724*	*0.411*	*0.853*
Childhood Cancer	Leukaemia	3/0.2	15.4 (3.2 to 45.0)	*Ref*	0.1 (-0.0 to 0.3)	*Ref*
	Hodgkin Lymphoma	8/0.1	81.3 (35.1 to 160.1)	6.1 (1.5 to 25.1)	0.9 (0.3 to 1.5)	6.6 (1.4 to 29.9)
	Non-Hodgkin Lymphoma	2/0.1	35.7 (4.3 to 128.8)	2.7 (0.4 to 16.6)	0.4 (-0.2 to 0.9)	2.9 (0.4 to 19.7)
	Central Nervous System	19/0.2	80.5 (48.4 to 125.7)	6.4 (1.8 to 22.6)	0.8 (0.4 to 1.2)	6.9 (1.7 to 27.3)
	Neuroblastoma	2/0.0	48.2 (5.8 to 174.3)	2.1 (0.3 to 13.1)	0.4 (-0.1 to 0.9)	2.1 (0.3 to 14.6)
	Retinoblastoma	0/0.1	-	-	-	-
	Wilms Tumour	6/0.1	76.0 (27.9 to 165.4)	3.8 (0.9 to 16.1)	0.6 (0.1 to 1.1)	4.0 (0.9 to 18.9)
	Bone Sarcoma STS	3/0.1[3]	21.6 (4.5 to 63.1)	1.5 (0.3 to 7.7)[3]	0.2 (-0.0 to 0.5)	1.6 (0.3 to 9.0)[3]
	Other	2/0.2	9.8 (1.2 to 35.5)	0.7 (0.1 to 4.6)	0.1 (-0.1 to 0.3)	0.7 (0.1 to 5.3)
	Not classifiable[†]	0/0.0	-	-	-	-
	$P_{heterogeneity}$		*0.001*	*<0.001*	*<0.001*	*<0.001*
Decade of Diagnosis	<1970	11/0.3	35.9 (17.9 to 64.3)	0.9 (0.4 to 2.2)	0.4 (0.1 to 0.6)	0.9 (0.4 to 2.1)
	1970–1979	12/0.3	39.4 (20.4 to 68.9)	*Ref*	0.4 (0.2 to 0.6)	*Ref*
	1980–1989	16/0.3	48.9 (27.9 to 79.4)	1.4 (0.6 to 3.0)	0.5 (0.2 to 0.7)	1.4 (0.7 to 3.2)
	>=1990	6/0.2	35.1 (12.9 to 76.4)	1.0 (0.3 to 3.1)	0.3 (0.1 to 0.6)	1.1 (0.4 to 3.5)
	P_{trend}		*0.761*	*0.624*	*0.966*	*0.381*
Attained Age	0–19 years	11/0.2	44.6 (22.3 to 79.9)	*Ref*	0.3 (0.1 to 0.4)	*Ref*
	20–29 years	18/0.5	37.6 (22.3 to 59.4)	0.8 (0.4 to 1.8)	0.5 (0.2 to 0.7)	1.7 (0.7 to 3.9)
	30+ years	16/0.4	41.7 (23.9 to 67.8)	1.0 (0.4 to 2.6)	0.5 (0.2 to 0.7)	1.9 (0.7 to 5.0)
	P_{trend}		*0.956*	*0.877*	*0.141*	*0.187*
Years from Diagnosis	5–14 years	17/0.5	36.8 (21.4 to 58.8)	*Ref*	0.3 (0.1 to 0.4)	*Ref*
	15–24 years	21/0.4	56.7 (35.1 to 86.7)	1.5 (0.7 to 3.0)	0.6 (0.3 to 0.9)	2.2 (1.1 to 4.3)
	25+ years	7/0.3	25.3 (10.2 to 52.2)	0.6 (0.2 to 1.8)	0.3 (0.1 to 0.5)	1.1 (0.4 to 3.0)
	P_{trend}		*0.597*	*0.563*	*0.564*	*0.491*

Abbreviations: O– observed number of STS, E – expected number of STS, SIR- standardised incidence ratio, AER- absolute excess risk, 95%CI- 95% confidence interval, RR – relative risk, RER – relative excess risk, ref – reference category

[1]Due to small numbers all Italian cohorts were grouped

[2]Due to small numbers all Nordic cohorts were grouped

[3]Due to small numbers bone sarcomas and STS were grouped

[†]Childhood cancer survivors diagnosed in Slovenia before 1983– excluded from multivariable analysis

* Model containing follow-up is adjusted for gender, country, age at diagnosis, childhood cancer diagnosis and decade of childhood cancer diagnosis. Model containing attained age is adjusted for gender, country, age at diagnosis, childhood cancer diagnosis and decade of childhood cancer diagnosis. Not classifiable tumours were excluded from multivariable analysis.

Table 5.9: Location of malignant peripheral nerve sheath tumours with regards to radiotherapy field (inside/outside) for original childhood cancer stratified by Neurofibromatosis status.

NEUROFIBROMATOSIS PRESENT			
Childhood Cancer	**Inside RT Field**	**Outside RT Field[$]**	**Unknown**
Leukaemia	0	0	0
Hodgkin Lymphoma	2 (100%)	0	0
Non-Hodgkin Lymphoma	0	0	0
Central Nervous System	5 (45%)	6 (55%)	2
Neuroblastoma	0	0	0
Retinoblastoma	0	0	0
Wilms tumour	2 (67%)	1 (33%)	0
Bone tumour	0	0	0
Soft-tissue sarcoma	2 (100%)	0	0
Other	1 (100%)	0	0
Total	12 (63%)	7 (37%)	2
NEUROFIBROMATOSIS ABSENT			
Childhood Cancer	**Inside RT Field**	**Outside RT Field**	**Unknown**
Leukaemia	1 (33%)	2 (67%)	0
Hodgkin Lymphoma	4* (80%)	1 (20%)	1[#]
Non-Hodgkin Lymphoma	1 (50%)	1 (50%)	0
Central Nervous System	1 (20%)	4 (80%)	1
Neuroblastoma	2 (100%)	0	0
Retinoblastoma	0	0	0
Wilms tumour	3 (100%)	0	0
Bone tumour	0	0	0
Soft-tissue sarcoma	1 (100%)	0	0
Other	1 (100%)	0	0
Total	14 (64%)	8 (36%)	2

* 1 has other genetic condition
[$] Includes those not receiving radiotherapy for the original childhood cancer.
[#]Unknown whether neurofibromatosis present

Table 5.10: Risk of all subsequent primary STS among 2,578 5-year survivors of retinoblastoma, by potential explanatory factors

Factor	Level	O/E	SIR (95% CI)	RR (95% CI)*	AER (95% CI)	RER (95% CI)
Overall	All combined	64/0.9	72.8 (56.1 to 93.0)		10.5 (7.9 to 13.1)	
Sex	Male	31/0.5	64.1 (43.5 to 90.9)	*Ref*	9.7 (6.2 to 13.2)	*Ref*
	Female	33/0.4	83.5 (57.5 to 117.3)	1.3 (0.8 to 2.2)	11.3 (7.4 to 15.2)	1.2 (0.7 to 2.0)
	$P_{heterogeneity}$		*0.288*	*0.255*	*0.555*	*0.496*
Country	France	7/0.1	133.3 (53.6 to 274.7)	*Ref*	18.9 (4.8 to 33.0)	*Ref*
	Hungary	2/0.0	137.7 (16.7 to 497.2)	1.4 (0.3 to 6.8)	13.1 (-5.2 to 31.3)	1.3 (0.3 to 6.4)
	Italy[1]	0/0.0	-	-	-	-
	Netherlands	3/0.0	391.9 (80.8 to 1145.2)	3.4 (0.9 to 13.4)	46.4 (-6.2 to 99.0)	3.5 (0.9 to 13.7)
	Nordic Countries[2]	11/0.3	42.0 (21.0 to 75.2)	0.3 (0.1 to 0.7)	6.4 (2.5 to 10.3)	0.3 (0.1 to 0.7)
	Slovenia	0/0.0	-	-	-	-
	Switzerland	0/0.0	-	-	-	-
	UK	41/0.5	82.4 (59.1 to 111.8)	0.5 (0.2 to 1.2)	12.1 (8.3 to 15.8)	0.5 (0.2 to 1.1)
	$P_{heterogeneity}$		*0.003*	*0.005*	*0.009*	*0.007*
Decade of Diagnosis	<1970	45/0.5	82.2 (59.9 to 110.0)	*Ref*	14.7 (10.4 to 19.1)	*Ref*
	≥1970	19/0.3	57.3 (34.5 to 89.5)	0.8 (0.4 to 1.5)	6.2 (3.4 to 9.1)	0.8 (0.4 to 1.6)
	P_{trend}		*0.186*	*0.446*	*0.001*	*0.558*
Attained Age	0–29 years	21/0.4	49.2 (30.4 to 75.2)	*Ref*	4.5 (2.6 to 6.5)	*Ref*
	30–39 years	21/0.2	90.3 (55.9 to 138.1)	1.7 (0.9 to 3.3)	21.7 (12.3 to 31.1)	4.7 (2.4 to 9.0)
	40+ years	22/0.2	100.2 (62.8 to 151.8)	1.8 (0.9 to 3.8)	40.8 (23.6 to 58.0)	8.7 (4.3 to 17.7)
	P_{trend}		*0.011*	*0.074*	*<0.001*	*<0.001*
Years from Diagnosis	5–24 years	18/0.4	50.1 (29.7 to 79.1)	*Ref*	4.3 (2.3 to 6.3)	*Ref*
	25–34 years	18/0.2	75.2 (44.6 to 118.8)	1.4 (0.7 to 2.7)	15.5 (8.2 to 22.7)	3.5 (1.8 to 6.9)
	35–44 years	17/0.2	93.1 (54.2 to 149.0)	1.6 (0.8 to 3.6)	30.1 (15.6 to 44.5)	6.8 (3.2 to 14.8)
	45+ years	11/0.1	113.1 (56.5 to 202.5)	1.9 (0.8 to 4.5)	57.7 (23.3 to 92.1)	12.7 (5.3 to 30.0)
	P_{trend}		*0.016*	*0.119*	*<0.001*	*<0.001*

Abbreviations: O – observed number of STS, E – expected number of STS, SIR- standardised incidence ratio, AER – absolute excess risk, RR- relative risk, RER- relative excess risk, 95%CI- 95% confidence interval, ref- reference category

[1]Due to small numbers all Italian cohorts were grouped

[2]Due to small numbers all Nordic cohorts were grouped

***** Model containing follow-up is adjusted for gender, country, childhood cancer and Decade of childhood cancer diagnosis. Model containing attained age is adjusted for gender, country, childhood cancer diagnosis and Decade of childhood cancer diagnosis. Not classifiable tumours were excluded from multivariable analysis.

Table 5.11: Risk of all subsequent primary leiomyosarcoma among 2,578 5-year survivors of retinoblastoma, by potential explanatory factors

Factor	Level	O/E	SIR (95% CI)	RR (95% CI)*	AER (95% CI)	RER (95% CI)
Overall	All combined	40/0.1	342.9 (245.0 to 466.9)		6.6 (4.6 to 8.7)	
Sex	Male	17/0.0	429.4 (250.1 to 687.4)	*Ref*	5.4 (2.8 to 8.0)	*Ref*
	Female	23/0.1	298.5 (189.2 to 447.9)	0.8 (0.4 to 1.5)	7.9 (4.7 to 11.2)	1.5 (0.8 to 2.8)
	$P_{heterogeneity}$		*0.253*	*0.424*	*0.232*	*0.208*
Country	France	5/0.0	1027.6 (333.7 to 2398.0)	*Ref*	13.6 (1.7 to 25.5)	*Ref*
	Hungary	1/0.0	1233.0 (31.2 to 6869.8)	1.4 (0.2 to 12.9)	6.6 (-6.3 to 19.5)	1.2 (0.1 to 11.1)
	Italy[1]	0/0.0	-	-	-	-
	Netherlands	0/0.0	-	-	-	-
	Nordic Countries[2]	5/0.0	143.2 (46.5 to 334.1)	0.1 (0.0 to 0.5)	3.0 (0.3 to 5.6)	0.2 (0.0 to 0.6)
	Slovenia	0/0.0	-	-	-	-
	Switzerland	0/0.0	-	-	-	-
	UK	29/0.1	401.8 (269.1 to 577.1)	0.4 (0.1 to 1.1)	8.6 (5.5 to 11.8)	0.4 (0.2 to 1.2)
	$P_{heterogeneity}$		*0.041*	*0.08*	*0.044*	*0.095*
Decade of Diagnosis	<1970	31/0.1	334.8 (227.5 to 475.2)	*Ref*	10.2 (6.6 to 13.8)	*Ref*
	≥1970	9/0.0	374.2 (171.1 to 710.3)	1.1 (0.4 to 3.1)	3.0 (1.0 to 5.0)	1.0 (0.4 to 2.7)
	P_{trend}		*0.769*	*0.84*	*<0.001*	*0.948*
Attained Age	0–29 years	7/0.0	267.8 (107.7 to 551.7)	*Ref*	1.5 (0.4 to 2.7)	*Ref*
	30–39 years	13/0.0	401.4 (213.7 to 686.5)	1.6 (0.6 to 4.5)	13.6 (6.2 to 21.0)	8.8 (3.3 to 23.5)
	40+ years	20/0.1	344.1 (210.2 to 531.4)	1.5 (0.5 to 4.6)	37.3 (20.9 to 53.7)	25.5 (9.1 to 71.2)
	P_{trend}		*0.599*	*0.465*	*<0.001*	*<0.001*
Years from Diagnosis	5–24 years	6/0.0	298.7 (109.6 to 650.2)	*Ref*	1.4 (0.3 to 2.6)	*Ref*
	25–34 years	11/0.0	380.9 (190.1 to 681.5)	1.3 (0.4 to 3.7)	9.5 (3.9 to 15.2)	6.3 (2.3 to 17.5)
	35–44 years	13/0.0	332.1 (176.8 to 567.9)	1.2 (0.4 to 3.9)	23.2 (10.5 to 35.8)	15.9 (5.2 to 48.3)
	45+ years	10/0.0	350.3 (168.0 to 644.3)	1.2 (0.4 to 4.1)	52.7 (20.0 to 85.5)	34.9 (10.8 to 112.8)
	P_{trend}		*0.858*	*0.827*	*<0.001*	*<0.001*

Abbreviations: O – observed number of STS, E – expected number of STS, SIR- standardised incidence ratio, AER – absolute excess risk, RR- relative risk, RER- relative excess risk, 95%CI- 95% confidence interval, ref- reference category

[1]Due to small numbers all Italian cohorts were grouped

[2]Due to small numbers all Nordic cohorts were grouped

* Model containing follow-up is adjusted for gender, country, childhood cancer and Decade of childhood cancer diagnosis. Model containing attained age is adjusted for gender, country, childhood cancer diagnosis and Decade of childhood cancer diagnosis. Not classifiable tumours were excluded from multivariable analysis.

Table 5.12: Risk of developing a subsequent primary STS among 69,460 5-year survivors of childhood cancer by potential explanatory factors (Excluding France).

Factor	Level	O/E	SIR (95% CI)	RR (95% CI)*	AER (95% CI)	RER (95% CI)*
Overall	All combined	253/17.7	14.3 (12.6,16.2)		2.3 (2.0,2.6)	
Sex	Male	135/9.6	14.0 (11.8,16.6)	1.0 (1.0,1.0)	2.3 (1.8,2.7)	1.0 (1.0,1.0)
	Female	118/8.1	14.7 (12.1,17.5)	1.1 (0.9,1.5)	2.3 (1.8,2.7)	1.0 (0.8,1.3)
	$P_{heterogeneity}$		0.7	0.358	0.965	0.984
Country	France		-	-	-	-
	Hungary	6/0.6	9.6 (3.5,20.9)	1.0 (1.0,1.0)	1.1 (0.1,2.0)	1.0 (1.0,1.0)
	Italy (PB)	12/1.0	11.8 (6.1,20.5)	1.3 (0.5,3.4)	1.6 (0.6,2.5)	1.3 (0.4,3.6)
	Italy (HB)	1/0.3	3.0 (0.1,16.6)	0.4 (0.0,3.1)	0.3 (-0.6,1.1)	0.3 (0.0,4.1)
	Netherlands	32/1.5	20.8 (14.2,29.4)	2.5 (1.0,6.1)	2.9 (1.9,4.0)	2.6 (1.0,6.7)
	Denmark	18/1.7	10.3 (6.1,16.3)	1.2 (0.5,3.1)	2.1 (1.0,3.1)	1.3 (0.5,3.6)
	Sweden	25/2.2	11.4 (7.4,16.8)	1.4 (0.5,3.5)	2.0 (1.1,2.8)	1.4 (0.5,3.9)
	Norway	9/1.0	9.0 (4.1,17.2)	1.1 (0.4,3.1)	1.5 (0.4,2.6)	1.1 (0.4,3.6)
	Finland	27/2.3	12.0 (7.9,17.4)	1.4 (0.6,3.6)	2.4 (1.4,3.3)	1.5 (0.6,4.1)
	Iceland	2/0.1	30.6 (3.7,110.7)	3.9 (0.8,19.9)	5.6 (-2.4,13.6)	4.4 (0.8,23.8)
	Slovenia	5/0.5	10.9 (3.6,25.5)	2.2 (0.6,8.0)	1.8 (0.1,3.6)	2.3 (0.6,8.9)
	Switzerland	9/0.6	14.5 (6.6,27.5)	1.7 (0.6,4.7)	1.8 (0.5,3.1)	1.5 (0.5,4.8)
	UK	107/5.8	18.4 (15.1,22.3)	1.7 (0.7,4.0)	2.7 (2.2,3.3)	1.7 (0.7,4.1)
	$P_{heterogeneity}$		0.015	0.083	0.047	0.151
Age at Diagnosis	0-4 yrs	116/5.2	22.3 (18.5,26.8)	1.0 (1.0,1.0)	2.6 (2.1,3.1)	1.0 (1.0,1.0)
	5-9 yrs	40/3.7	10.9 (7.8,14.8)	0.9 (0.6,1.3)	1.5 (1.0,2.1)	0.9 (0.6,1.4)
	10-14 yrs	62/4.8	12.9 (9.9,16.5)	1.1 (0.7,1.7)	2.4 (1.8,3.1)	1.1 (0.7,1.8)
	15-19yrs	35/4.0	8.8 (6.1,12.2)	0.9 (0.5,1.6)	2.0 (1.3,2.8)	0.9 (0.5,1.6)
	P_{trend}		<0.001	0.971	0.318	0.953
Type of Childhood Cancer	Leukaemia	19/2.8	6.8 (4.1,10.6)	1.0 (1.0,1.0)	0.7 (0.3,1.1)	1.0 (1.0,1.0)
	Hodgkin Lymphoma	29/1.6	17.8 (11.9,25.6)	3.1 (1.6,5.6)	3.3 (2.0,4.6)	3.3 (1.7,6.6)
	Non-Hodgkin Lymphoma	6/0.9	6.5 (2.4,14.1)	1.0 (0.4,2.7)	1.0 (0.1,1.9)	1.0 (0.3,3.0)
	Central Nervous System	39/3.9	10.1 (7.2,13.8)	1.7 (1.0,3.0)	1.6 (1.0,2.2)	1.8 (0.9,3.4)
	Neuroblastoma	11/0.5	20.8 (10.4,37.3)	3.0 (1.4,6.4)	2.4 (0.9,3.9)	3.2 (1.4,7.4)
	Retinoblastoma	57/0.8	69.0 (52.2,89.4)	10.8 (6.1,19.1)	9.9 (7.3,12.6)	12.1 (6.4,23.0)
	Wilms Tumour	27/1.0	26.5 (17.4,38.5)	3.9 (2.1,7.1)	3.4 (2.1,4.7)	4.3 (2.2,8.4)
	Bone Sarcoma	18/1.0	18.7 (11.1,29.5)	3.1 (1.6,6.1)	3.7 (1.9,5.5)	3.4 (1.6,7.2)
	Soft-Tissue Sarcoma	18/1.3	13.5 (8.0,21.3)	2.2 (1.2,4.3)	2.3 (1.1,3.4)	2.4 (1.2,5.0)
	Other	28/3.5	8.0 (5.3,11.6)	1.5 (0.8,2.7)	1.5 (0.9,2.1)	1.5 (0.8,3.1)
	Not classifiable[†]	1/0.3	3.7 (0.1,20.8)		0.6 (-1.0,2.3)	
	$P_{heterogeneity}$		<0.001	<0.001	<0.001	<0.001
Decade of Diagnosis	<1970	100/6.4	15.6 (12.7,19.0)	1.2 (0.8,1.7)	3.6 (2.8,4.3)	1.1 (0.8,1.6)
	1970-1979	63/4.8	13.1 (10.1,16.8)	1.0 (1.0,1.0)	2.1 (1.5,2.7)	1.0 (1.0,1.0)
	1980-1989	54/4.4	12.3 (9.3,16.1)	1.0 (0.7,1.4)	1.6 (1.1,2.0)	1.0 (0.7,1.5)
	>=1990	36/2.1	17.2 (12.1,23.9)	1.4 (0.9,2.2)	1.8 (1.2,2.4)	1.5 (0.9,2.4)
	P_{trend}		0.641	0.887	<0.001	0.756
Attained Age	0-19 rs	58/3.1	19.0 (14.4,24.6)	1.0 (1.0,1.0)	1.4 (1.0,1.8)	1.0 (1.0,1.0)
	20-29 yrs	79/5.3	15.0 (11.9,18.7)	0.9 (0.6,1.2)	2.0 (1.6,2.5)	1.6 (1.1,2.4)
	30-39 yrs	69/4.8	14.5 (11.3,18.3)	0.8 (0.5,1.2)	3.3 (2.5,4.1)	2.7 (1.7,4.1)
	40+ yrs	47/4.6	10.2 (7.5,13.6)	0.6 (0.3,0.9)	4.1 (2.8,5.4)	3.3 (2.0,5.5)
	P_{trend}		0.003	0.026	<0.001	<0.001
Years from Diagnosis	5-14 yrs	96/5.5	17.4 (14.1,21.3)	1.0 (1.0,1.0)	1.7 (1.3,2.0)	1.0 (1.0,1.0)
	15-24 yrs	67/5.4	12.4 (9.6,15.8)	0.7 (0.5,0.9)	2.0 (1.5,2.5)	1.1 (0.8,1.6)
	25-34 yrs	43/4.0	10.8 (7.8,14.5)	0.5 (0.3,0.8)	2.8 (1.9,3.7)	1.5 (1.0,2.3)
	35-44 yrs	36/2.1	17.3 (12.1,24.0)	0.7 (0.4,1.1)	7.1 (4.7,9.6)	3.5 (2.1,5.7)
	45+yrs	11/0.7	15.5 (7.8,27.8)	0.5 (0.3,1.1)	9.6 (3.6,15.7)	4.3 (2.1,8.8)
	P_{trend}		*0.447*	*0.013*	*<0.001*	*<0.001*

Abbreviations: O– observed number of STS, E – expected number of STS, SIR- standardised incidence ratio, AER- absolute excess risk, 95%CI- 95% confidence interval, PB- population based, HB- hospital based, RR- relative risk, RER- relative excess risk, ref- reference category

[†]Childhood cancer survivors diagnosed in Slovenia before 1983– excluded from multivariable analysis

* Model containing years from diagnosis was adjusted for gender, country, age at diagnosis, childhood cancer diagnosis and decade of childhood cancer diagnosis. Model containing attained age was adjusted for gender, country, age at diagnosis, childhood cancer diagnosis and decade of childhood cancer diagnosis. Not classifiable tumours were excluded from multivariable analysis.

Chapter 6

Risk of malignant breast cancer among 31,722 female survivors of childhood cancer in Europe

6.1 ABSTRACT

Background: Female survivors of childhood cancer exposed to chest irradiation are at an increased risk of subsequent primary breast neoplasms (breast SPNs). Risk-based surveillance is recommended for young women after chest irradiation, until at least age 50. For women aged over 40 years, however, little empiric information on the magnitude of breast cancer risk is available.

Methods: We calculated standardised incidence ratios (SIRs) and absolute excess risks (AERs) to quantify the risk of malignant breast cancer in a large, pan-European childhood cancer survivor population of 31,722 female survivors where 20% were aged over 40 years.

Results: Overall, 411 breast SPNs were observed compared to 146 expected (SIR=2.8, CI=2.5-3.1). Highest SIRs were observed after Hodgkins lymphoma (SIR=11.3, CI=9.4-13.5), Wilms tumour (SIR=4.5, CI=3.2-6.2) and bone sarcoma (SIR=4.6, CI=3.3-6.1). Beyond age 50 years, the SIR remained significantly elevated (SIR=1.5; CI=1.1-1.9). The AER increased with increasing attained age until age 40 years and remained significantly elevated thereafter (AER=14, CI=9-20 at age 40-49 years and AER=13, CI=3-23 at 50+ years). Among survivors of Hodgkin lymphoma and Wilms tumour the AERs increased with increasing attained age, and showed no sign of a decline with 99 (CI=66-132) and 26 (CI=1-50) excess breast cancers per 10,000 survivors per year beyond age 40 years, respectively. Among sarcoma survivors, the AER increased significantly with attained age until age 40 years ($P_{trend}<0.001$) and remained significantly elevated thereafter (AER=25, CI=16-35 at age 30-39 years and AER=14, CI=2-26 at age 40+ years). The SIR and AER did not vary across diagnosis decades (≤1970, 1970-1979, 1980-1989, 1990-2008) ($P_{trend}=0.152$ and $P_{trend}=0.119$).

Conclusion: Wilms tumour, Hodgkin lymphoma and sarcoma survivors have an increased number of excess breast SPNs beyond age 40 years. We provide new empiric evidence on the

long-term risks of breast cancer that should aid in revising the current international breast cancer surveillance guidelines for survivors of cancer diagnosed during childhood or adolescence.

6.2 INTRODUCTION

Over the last few decades, advances in the treatment of childhood cancer have resulted in a substantial increase in survival from childhood cancer over time. In Europe, 80% of childhood cancer patients can now expect to survive at least five years[198]. However, the growing survivor population is at risk of long-term adverse health outcomes[50, 92-95]. Subsequent primary neoplasms (SPNs) are one of the most severe adverse health outcomes and account for 50% of the total excess mortality beyond 45 years from diagnosis of childhood cancer[92].

Besides basal cell carcinoma of the skin, breast cancer is the most commonly diagnosed SPN among female childhood cancer survivors[97-99, 102, 104]. Treatment for childhood cancer with high-dose chest radiotherapy is an established risk factor for the development of breast SPNs[31, 55, 57, 122-126]. Current long-term follow-up guidelines recommend yearly breast cancer surveillance for female childhood cancer survivors aged 25-50 years with a history of high-dose chest radiotherapy [58]. It is unclear, though, if continuation of this intense surveillance schedule is warranted as women age. In addition, recommendations for screening of individuals aged 40-50 years are based on studies with small number of person-years and breast events after age 40 years[57, 98, 99, 123], particularly after specific childhood cancers (e.g. Wilms tumour) [31, 125, 215]. If the excess risk were to decrease with increasing attained age, it may be appropriate to stop the high-risk screening program at a certain age[19], and rather, refer women to regular, population-based screening programs for post-menopausal women in effect

in many western countries[216]. However, few studies have investigated whether the number of breast SPNs remains increased among ageing survivors[98, 99, 123]. Breast cancer is most common after age 50 in the general population, therefore if any increased risk of breast SPNs sustains into older age among childhood cancer survivors this could result in a large number of survivors developing a breast SPN.

Increased awareness of late effects among childhood cancer survivors has resulted in smaller fields and lower doses of radiotherapy applied in more recent diagnosis eras[217]; therefore it is not inconceivable that survivors treated more recently are at lower risk of developing a breast SPN than survivors treated in earlier decades[31].

We investigated the risk of developing a breast SPN among the largest cohort of childhood and adolescent cancer survivors. This study provides over 57,000 person-years beyond age 40 years to determine if the increased risk of developing a breast SPN persists when the background risk in the general population starts to increase. The specific aims were three-fold: 1) quantify risk of breast SPNs among survivors of all and specific childhood cancers; 2) quantify risk of breast SPNs among an ageing survivor population; and 3) ascertain if the risk of breast SPNs is lower among childhood cancer survivors treated in recent diagnosis eras.

6.3 METHODS

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

PanCareSurFup combines data from 13 European cohorts of childhood and adolescent cancer survivors to form a pan-European cohort study to investigate the long-term risk of adverse

health outcomes among this population. Ethical approval for the study was obtained from the appropriate bodies within each participating country. Data were obtained from both population-based cohorts and individual treatment centres to provide a pan-European cohort consisting of 69,460 5-year survivors of cancer diagnosed before age 20 years between 1940 and 2011. Ascertainment of the cohort has been described in-depth previously (see Chapter 5). In short, individuals were eligible to be included in the cohort if the first primary neoplasm (FPN): (1) could be grouped according to the International Classification of Childhood Cancers (ICCC)[79], (2) was of a malignant behaviour (with the exception of intracranial tumours, for which any behaviour was allowed), (3) and was not a Langerhans cell histiocytosis, myelodisplastic syndrome, chronic myeloproliferative and lymphoproliferative disorder or an immune proliferative disease, as these were not ascertained by all 13 individual cohorts. For the current analyses, males were excluded, resulting in 31,722 female childhood cancer survivors eligible for analyses.

6.3.2 Subsequent primary breast cancer ascertainment

SPNs were ascertained through several different methods including: linkage with population-based cancer registries (Denmark, Finland, Iceland, Italy, Netherlands, Norway, Slovenia, Sweden, Switzerland, and UK), long-term follow-up clinics (France, Hungary, Netherlands, Slovenia and Switzerland), questionnaires to survivors (France and Hungary), medical records/hospital data (France, Hungary, Italy, Netherlands and Slovenia), national mortality records (France, Italy and Switzerland) and the health insurance reimbursement database (France). The primary method of validation was through pathology reports or in their absence other means of clinical diagnosis. A breast SPN was defined as any tumour of malignant behaviour that was not a metastases or recurrence of the childhood cancer (defined as a

different histological classification) that was located within the breast. Breast site was defined using the International Classification of Diseases (ICD) — C50 (ICD-10), 174 (ICD-8/9) and 170 (ICD-7)[185-187].

6.3.3 General population cancer incidence rates

Cancer incidence rates for the general population were ascertained from the Cancer Incidence in Five Continents CI5PLUS dataset[218]. Rates were available per 5-year age strata and 1-year calendar period strata for France (1975-2007), Italy (1978-2007), the Netherlands (1989-2007), Denmark (1953-2007), Sweden (1958-2007), Norway (1953-2007), Finland (1953-2007), Iceland (1958-2007), Slovenia (1963-2007), Switzerland (1970-2007) and the UK (1975-2007). Rates were unavailable for Hungary; but because of the close geographical proximity surrogate Italian rates were used. When the year of cancer diagnosis was outside of the available range of the general population cancer rates, the rate for the closest available year was used.

6.3.4 Statistical analysis

Childhood cancer survivors were at risk of a breast SPN from the date of 5-year survival after childhood cancer until the first occurrence of death, emigration, or the study end date for the respective cohort. Contralateral breast SPNs per individual were allowed for all analyses with the exception of cumulative incidence where the first event only was included. The expected number of SPNs was calculated by multiplying the total person-years stratified by age (5-year bands) and calendar year (1-year bands) by the corresponding general population breast cancer incidence rates. Standardised incidence ratios (SIRs) were derived as the observed number of breast SPNs divided by the expected number of breast SPNs. Absolute excess risks

(AERs) were calculated as the observed number of breast SPNs minus the expected number of breast SPNs divided by the accumulated person-years, and then multiplied by 10,000[153]. SIRs and AERs were stratified by childhood cancer, country and attained age. Poisson regression models incorporating the expected number of breast SPNs were used to calculate the SIR and AER by continuous attained age (1-year categories fitted as a restricted cubic spline) and results were shown graphically.

The effect of diagnosis era (<1970/1970-79/1980-89/1990-99/≥2000) on the development of breast SPNs was investigated using multivariable Poisson regression incorporating the expected number of breast SPNs to calculate the relative risk (RR) and relative excess risk (RER) adjusting for childhood cancer type (among all survivors only), age at diagnosis, country, and attained age (1-year categories fitted as a restricted cubic spline)[154]. The RR can be interpreted as the ratio of SIRs adjusting for potential explanatory factors. The RER can be interpreted as the ratio of AERs adjusting for potential explanatory factors. The cumulative incidence at age 60 years for all childhood cancer survivors and age 50 years for subgroups of childhood cancer survivors was calculated treating death as a competing risk[189].

All analyses were also conducted separately for survivors of Hodgkin lymphoma, Wilms tumour, sarcoma (bone & soft-tissue), leukaemia, and all other childhood cancers. These groups were selected based on the high risk of breast cancer associated with chest radiotherapy (Hodgkin lymphoma[31, 55, 57, 122, 123, 126] and Wilms tumour[57, 123, 126]) and chemotherapy (sarcoma and leukaemia)[126, 219, 220] reported in previous studies.

To confirm the robustness of all of the multivariable Poisson regression models with attained age fitted as a restricted cubic spline, Cox regression models with attained age as the time metric were also fitted. In addition stratified Cox regression models with country as strata were also fitted. Similar results were obtained for all three model types (not shown); therefore, only the Poisson regression models are reported. Tests for trend and heterogeneity were calculated using likelihood-ratio tests comparing the deviance of a multivariable model including the factor of interest (with median values at each level of the relevant factor— fitted as linear for trend and categorical for heterogeneity) to the deviance of a multivariable model without the factor of interest. All p-values<0.05 were taken as statistically significant. All analyses were conducted in Stata 14.1

6.4 RESULTS

6.4.1 Cohort characteristics

In total, 411 breast SPNs (excluding in situ-tumours) were diagnosed in 385 of the 31,722 female childhood cancer survivors in the cohort (Table 6.1). Total follow-up from 5-year survival was 524,884 person-years. The median age at last follow-up was 29 years (range: 5-79) and the median age at diagnosis of a breast SPN was 39 years (range: 15-71). Of the survivors, 13% had an attained age at exit of 40-49 years and 7% had an attained age of 50 years or older; beyond age 40 years almost 57,000 person-years of follow-up were available. With respect to childhood cancer diagnosis era, 14% were diagnosed before 1970, 20% between 1971-1979, 30% between 1980-1989, 27% between 1990-1999 and 10% in 1990 or after. The most common type of breast cancer was infiltrating duct carcinoma (72%) followed by lobular carcinoma (8%) (Table 6.2).

6.4.2 Risk compared to the general population

Childhood cancer survivors had a 3-fold risk of developing a breast SPN compared to that expected from the general population (SIR=2.8, 95% confidence interval [CI]=2.5-3.1), corresponding to an AER of 5 per 10,000 person-years (CI=4.3-5.8). This implies that, for each additional year of follow-up, on average, a new excess breast SPN developed in 5 of 10,000 female 5-year childhood cancer survivors (Table 6.3). Survivors of each type of childhood cancer (where observed≥10) had a significantly increased risk of developing a breast SPN than the general population, except CNS tumour survivors (SIR=1.0, CI=0.7-1.4). Survivors of Hodgkin lymphoma, bone sarcoma and Wilms tumour had the greatest risk of developing a breast SPN than in the general population with SIRs of 11.3 (CI=9.4-13.5), 4.6 (CI=3.3-6.1) and 4.5 (CI=3.2-6.2), respectively. With regards to country specific risks, SIRs were highest for Italy-HB (SIR=14.0, CI=7.4-23.9), Hungary (SIR=6.7, CI=2.7-13.8) and the Netherlands (SIR=5.8, CI=4.2-7.9) (Figure 6.1, Table 6.4). There was significant heterogeneity in the RR between countries ($P_{heterogeneity}<0.001$); when the UK was taken as baseline the RR was significantly higher for survivors in France (RR=1.6, CI=1.2-2.3), Italy-HB (RR=2.5, CI=1.4-4.6), the Netherlands (RR=1.6, CI=1.0-2.3) and Finland (RR=1.8, CI=1.2-2.5) (Table 6.4). However, when these countries were excluded there was no significant heterogeneity in breast cancer risk between countries ($P_{heterogeneity}=0.232$). In the entire cohort, cumulative incidence at age 50 years was 3.7% and at age 60 years was 6.0%, whereas 1.9% and 4.4% were expected, respectively (Table 6.3). Cumulative incidence at age 50 years was highest for survivors of Hodgkin lymphoma (12.5%), bone sarcoma (6.1%), retinoblastoma (4.5%), leukaemia (4.4%) and Wilms tumour (4.2%) (Table 6.3, Figure 6.2).

6.4.3 Breast cancer risk by attained age

Among all childhood cancer survivors, the SIR for breast SPNs decreased significantly with increasing attained age (P_{trend}<0.001) (Figure 6.3A). The SIR decreased from 7.8 (CI=5.8-10.2) at age 20-24 years to 1.5 (CI=1.1-1.9) beyond age 50 years. Statistically significant decreasing trends in SIRs with increasing attained age were observed among Hodgkin lymphoma, Wilms tumour and sarcoma survivors (Table 6.5). SIRs decreased from 27 to 7 among Hodgkin lymphoma survivors aged 5-29 and ≥40 years (P_{trend}<0.001). Within the same attained age groups, SIRs decreased from 9.3 to 2.5 among Wilms tumour survivors (P_{trend}=0.020) and from 12.2 to 1.7 among sarcoma survivors (P_{trend}<0.001).

Among all childhood cancer survivors, the AER increased significantly with increasing attained age until age 40 (P_{trend}<0.001), and remained significantly elevated thereafter (see Figure 6.3B). For each additional year of follow-up, a new excess breast SPN developed in 3 (CI=2-3), 14 (CI=11-16), 14 (CI=9-20) and 13 (CI=3-23) of 10,000 childhood cancer survivors aged 20-29, 30-39, 40-49 and aged 50 or older, respectively. Significant increasing trends in the AER of breast cancer with increasing attained age were observed among Hodgkin lymphoma and Wilms tumour survivors (both P_{trend}<0.001) (Table 6.5). For each additional year of follow-up, a new excess breast SPN developed in 99 (CI=66-132) and 25 (CI=1-50) of 10,000 Hodgkin lymphoma and Wilms tumour survivors aged 40 or older, respectively. Among sarcoma survivors, the AER increased significantly with attained age until age 40 (P_{trend}<0.001) and remained significantly elevated thereafter. For each additional

year of follow-up a new excess breast SPN developed in 25 (CI=16-35) and 14 (CI=2-26) of 10,000 sarcoma survivors aged 30-39 and aged 40 or older, respectively.

6.4.4 Breast cancer risk by diagnosis era (1940-1969/1970-1979/1980-1989/1990-2008)

The multivariable Poisson regression revealed that RRs and RERs did not differ significantly across the diagnosis eras for survivors of all childhood cancer or survivors of specific FPNs including Hodgkin lymphoma, Wilms tumour, sarcoma or leukaemia (all $P_{trend}>0.05$) (Table 6.6).

6.5 DISCUSSION

6.5.1 Main findings

This is the largest cohort study to assess the long-term risk of malignant breast SPNs among female childhood cancer survivors, with 31,722 5-year survivors, 524,884 person-years at risk and 411 observed breast SPNs. Beyond age 40 years more than 57,000 person-years accrued enabling robust estimates of excess risks to be reported—a research priority identified by the International Guideline Harmonisation Group (IGHG), a consortium of experts aiming to harmonise breast cancer surveillance guidelines for childhood, adolescent and young adult cancer survivors[58].

Here we show that among childhood cancer survivors the excess risk of breast cancer remains increased beyond age 50 years—the number of excess breast SPNs increases until age 40 years and remains significantly elevated thereafter. After each of Hodgkin lymphoma and Wilms tumour the excess number of breast SPNs increases with increasing attained age. Among sarcoma survivors, the AER increases significantly with attained age until age 40 and

remains significantly elevated thereafter. Beyond age 40 years, 99, 26 and 14 excess breast SPNs per 10,000 survivors per year were observed among survivors of Hodgkin lymphoma, Wilms tumour and sarcoma, respectively. Multivariable regression also revealed that breast SPN risk does not differ across the diagnosis eras (1940-1969, 1970-1979, 1980-1989, 1990-2008), regardless of childhood cancer type; so, despite substantial adaptations to radiotherapy practices, women treated for childhood cancer in recent decades *did not* have a significantly lower risk of developing a breast SPN than individuals treated in earlier diagnosis eras.

6.5.2 Previous studies

The British Childhood Cancer Survivor Study (BCCSS)[98]—which contributes data to the current study—did not observe a significantly increased risk of breast SPNs among childhood cancer survivors aged over 50 years (SIR=1.0, CI=0.6-1.8). A Nordic study[100]—again which contributes data to the current study— reported an increased risk of breast cancer among lymphoma survivors aged over 40 years (SIR=5.9, CI=3.9-8.5), but not among any other childhood cancer survivor. By combining 13 European cohorts of cancer survivors, the PanCareSurFup Cohort Study provides a large number of breast SPNs and person-years of follow-up beyond age 40 years; we were able to detect a 2-fold (CI=1.7-2.4) and 1.5-fold (CI=1.1-1.9) excess risk of breast SPNs among survivors aged 40-49 years and at least 50 years, respectively. This is lower than observed in the North American Childhood Cancer Survivor Study (CCSS)[99], where 5.5-fold (CI=4.5-6.7) risk beyond age 40 years was reported. Due to differing diagnosis periods (PanCareSurFup=1940-2008; CCSS=1970-1986) thus shorter follow-up among the CCSS, the childhood cancer survivors reaching age 40 in the CCSS cohort mainly represent cancers diagnosed in older children such as Hodgkin lymphoma and sarcoma, which are known to have a high risk of breast SPNs, which may in

part explain the higher risk observed among the CCSS than in this study. In addition the CCSS does not include survivors of retinoblastoma or 'other' childhood cancers. Due to the difference in follow-up, childhood cancer types and diagnostic period between the CCSS and PanCareSurFup, the results are not directly comparable. Therefore we conducted a sensitivity analysis, restricting to survivors who were diagnosed with childhood cancer (excluding retinoblastoma and 'other' childhood cancers) between 1970 and 1986 (results not shown). The SIR beyond age 40 years was 3.7 (CI=2.8-4.8), which is closer to the SIR reported by the CCSS[99].

In more recent decades, treatment of childhood cancer has turned to lower doses of radiotherapy and smaller radiation fields in order to optimize survival and reduce the risk of adverse health outcomes such as breast SPNs[217, 221]. However, among this cohort, the risk of breast SPNs did not decrease with more recent diagnosis (1940-2008), regardless of childhood cancer type. A Dutch study of survivors of Hodgkin lymphoma diagnosed aged 15-50 years also reported that the risk of breast cancer did not decrease with more recent diagnosis decade (1965-2000)[36]. Several studies have reported that reducing the volume of breast tissue that is irradiated in supradiagphragmatic fields results in a lower risk of breast SPNs[36, 123]. This reduction in volume of irradiated breast tissue may not have been used widely enough for a lower risk in more recent diagnosis decades to be observed in our cohort. Another potential explanation could be an increase in breast SPNs detected by clinical surveillance (e.g. Hodgkin lymphoma survivors recalled for breast screening) in recent diagnosis periods—the Dutch Hodgkin lymphoma study reported that the proportion of breast SPNs detected by screening increased from 30% before 2001, to 61% after 2001[36]. Prior to the published guidelines on breast screening, some late effect clinics have been advising

childhood cancer survivors to attend breast screening prior to the start of regular post-menopausal screening in the general population since the early 2000s[222, 223]. Therefore these screening-detected breast SPNs may be "picked up" earlier than they would have been in previous decades.

Exposure to chest irradiation is an established risk factor for breast SPNs in childhood cancer survivors [31, 55, 57, 122-126]; and largely explains the increased risk of breast SPNs among survivors of Hodgkin lymphoma and Wilms tumour who are often treated with mantel field radiotherapy and whole lung irradiation for lung metastases, respectively [31, 38, 55, 57, 123, 224, 225]. The effects of chemotherapy on the risk of breast SPNs are more uncertain. Previous studies have reported that treatment with alkylating agents for Hodgkin lymphoma can cause ovarian damage and consequently reduced hormonal stimulation and reduced risk of breast SPNs[55, 56]. Studies among all childhood cancer survivors did not find any significant associations between specific chemotherapeutic agents and breast cancer risk[57], although two recent studies have reported a dose-response relationship between alkylators and anthracyclines and the risk of breast SPNs among survivors of sarcoma and leukaemia [219, 220]. In addition, a genetic predisposition to cancer may increase the risk of breast cancer among some childhood cancer survivors. Sarcoma, leukaemia and breast cancer are known to be associated with Li Fraumeni Syndrome, a genetic syndrome where a germline mutation in the TP53 gene is present[226]. Therefore the increased risk of breast SPNs among the sarcoma and leukaemia survivors in the PanCareSurFup cohort may be partly explained by genetic predisposition.

6.5.3 Clinical Implications

The IGHG consortium recommend yearly breast screening to female childhood cancer survivors treated with chest radiotherapy (≥20Gy) who have reached age 50 years, however more evidence is required to justify recommending this intense yearly screening in this population rather than recommending attending regular population-based screening programs[58]. In addition, previous studies reporting risks after age 40 years for specific childhood cancers groups have been based on small number of events and person-years of follow-up [31, 57, 98, 99, 123, 125, 215]. This study provides evidence that Hodgkin lymphoma, Wilms tumour and sarcoma survivors have substantially increased excess numbers of breast SPNs beyond age 40 years. Our study provides evidence that should aid in revising and updating the current guidelines. However, studies including detailed information on cumulative doses of chest irradiation, in addition to cumulative chemotherapy exposures, among this ageing cancer survivor population are needed to provide more conclusive evidence.

6.5.4 Limitations

A limitation of this study is the lack of detailed treatment information; which prevents investigations into dose-response relationships between cumulative radiotherapy and chemotherapy doses and the associated risk of breast SPNs. However we provide risk estimates beyond age 50 years, and highlight the childhood cancer groups who are still at an increased risk of breast SPNs later in life, thus provide a basis for future studies.

A potential limitation is the observed heterogeneity between contributing cohorts included in PanCareSurFup. When France, Italy-PB, Netherlands and Finland were excluded, there was no significant heterogeneity in RR of breast SPNs between countries ($P_{heterogeneity}$=0.232).

However, the risk estimates produced from the stratified Cox regression models with country as strata, were very similar to the Poisson models that did not stratify by country (country included as categorical variable), suggesting that any heterogeneity between countries did not have a large effect on the overall risks of breast SPNs in the PanCareSurFup cohort. A large proportion of the French cohort attended two main treatment centres which are international referral centres for metastatic or otherwise difficult cancers, thus likely received high cumulative doses of radiotherapy. Clinical follow-up centres in the Netherlands and Italy-HB have invited survivors treated with high-dose chest radiotherapy to be screened for breast cancer since the early 2000s, therefore may diagnose breast SPNs earlier than if screening had not taken place[222].

6.6 CONCLUSIONS

This large pan-European study provides evidence that the excess number of breast SPNs remains substantially increased among Hodgkin lymphoma, Wilms tumour and sarcoma survivors beyond 40 years of age. We provide new empiric evidence on the long-term risks of breast cancer that should aid in revising the current international breast cancer surveillance guidelines for survivors of cancer diagnosed during childhood or adolescence.

Table 6.1: Cohort characteristics of whole cohort and number of breast cancers

	Total number of individuals		Number of Breast Cancers	
	n	%	n	%
Overall	31,722	100.0	411	100.0
Country				
France	1,407	4.4	59	14.4
Hungary	2,156	6.8	9	2.2
Italy PB	3,389	10.7	17	4.1
Italy HB	682	2.2	14	3.4
Netherlands	2,682	8.5	47	11.4
Denmark	10,809	6.8	34	8.3
Sweden	3,688	11.6	36	8.8
Norway	1,793	5.7	12	2.9
Finland	3,049	9.6	7	18.5
Iceland	123	0.4	0	0.0
Slovenia	560	1.8	6	1.5
Switzerland	1,954	6.2	6	1.5
UK	8,083	25.5	95	23.1
Childhood Cancer Diagnosis				
Leukemia	7,631	24.1	24	5.8
Hodgkins Disease	2,397	7.6	122	29.7
Non-Hodgkin Lymphoma	1,041	3.3	16	3.9
Central Nervous System Tumour	6,516	20.5	33	8.0
Neuroblastoma	1,551	4.9	7	1.7
Retinoblastoma	1,233	3.9	18	4.4
Wilms Tumour	2,363	7.5	37	9.0
Bone Tumour	1,417	4.5	45	11.0
Soft-Tissue Sarcoma	1,976	6.2	33	8.0
Other	5,432	17.1	71	17.3
Not in ICCC*	165	0.5	5	1.2
Decade of Childhood Cancer Diagnosis				
<1970	4,302	13.6	165	40.2
1970-1979	6,199	19.5	136	33.1
1980-1989	9,447	29.8	83	20.2
1990-1999	8,693	27.4	25	6.1
>=2000	3,081	9.7	2	0.5
Age at Childhood Cancer Diagnosis				
0-4 years	12,344	38.9	68	16.6
5-9 years	6,684	21.1	45	11.0
10-14 years	7,221	22.8	173	42.1
15-19 years	5,473	17.3	125	30.4
Attained Age at Exit				
0-29 years	17,306	54.6	55	13.4
30-39 years	8,044	25.4	175	42.6
40-49 years	4,043	12.8	116	28.2
50+ years	2,329	7.3	65	15.8

Abbreviations: PB- population based, HB- hospital based, ICCC- international classification of childhood cancer.
*Not in ICCC- Survivors diagnosed before 1983 in Slovenia were classified in ICD7 and thus could not be converted to ICCC.

Table 6.2 Morphology of subsequent primary breast neoplasms

Morphology	Description	N	%
85003	Infiltrating duct carcinoma, NOS	293	71.3
85203	Lobular carcinoma, NOS	35	8.5
81403	Adenocarcinoma, NOS	21	5.1
80103	Carcinoma, NOS	20	4.9
85223	Infiltrating duct and lobular carcinoma	8	2.0
85233	Infiltrating duct mixed with other types of carcinoma	5	1.2
84803	Mucinous adenocarcinoma	3	0.7
85013	Comedocarcinoma, NOS	3	0.7
85103	Medullary carcinoma, NOS	3	0.7
85213	Infiltrating ductular carcinoma	3	0.7
90203	Phyllodes tumour, malignant	3	0.7
80003	Neoplasm, malignant	2	0.5
80333	Pseudosarcomatous carcinoma	1	0.2
80823	Lymphoepithelial carcinoma	1	0.2
80953	Metatypical carcinoma	1	0.2
81413	Scirrhous adenocarcinoma	1	0.2
81903	Trabecular adenocarcinoma	1	0.2
85123	Medullary carcinoma with lymphoid stroma	1	0.2
85133	Atypical medullary carcinoma	1	0.2
85403	Paget's disease, mammary	1	0.2
85413	Paget's disease and infiltrating duct carcinoma of breast	1	0.2
85433	Paget's disease and intraductal carcinoma of breast	1	0.2
88013	Spindle cell sarcoma	1	0.2
Unknown	Unknown	1	0.2

Abbreviations: NOS- not otherwise specified

Table 6.3 – Standardised incidence ratios, absolute excess risks and cumulative incidence stratified by childhood cancer diagnosis

Childhood Cancer	Median Attained Age	O/E	SIR (95% CI)	AER (95% CI)	Cumulative Incidence at age 50 years (95%CI)
All Childhood Cancer	28.8	411/146.0	2.8 (2.5,3.1)	5.0 (4.3,5.8)	50 years: 3.7 (3.2,4.1) 60 years: 6.0 (5.3,7.0)
Leukaemia	24.6	24/9.4	2.6 (1.6,3.8)	1.4 (0.5,2.3)	4.4 (1.5,10.0)
Hodgkin Lymphoma	31.7	122/10.8	11.3 (9.4,13.5)	34.6 (27.9,41.4)	12.5 (9.8,15.5)
Non Hodgkin Lymphoma	30.3	16/5.4	3.0 (1.7,4.8)	6.3 (1.6,10.9)	4.2 (1.9,7.7)
Central Nervous System Tumour	28.4	33/32.0	1.0 (0.7,1.4)	0.1 (-1.0,1.1)	1.0 (0.6,1.5)
Neuroblastoma	23.5	7/3.7	1.9 (0.8,3.9)	1.2 (-0.7,3.1)	-
Retinoblastoma	30.2	18/6.4	2.8 (1.7,4.4)	4.0 (1.1,6.9)	4.5 (2.5,8.1)
Wilms Tumour	27.8	37/8.2	4.5 (3.2,6.2)	6.1 (3.6,8.7)	4.2 (2.6,6.4)
Bone Sarcoma	31.8	45/9.8	4.6 (3.3,6.1)	15.0 (9.4,20.6)	6.1 (4.1,8.5)
Soft Tissue Sarcoma	30.7	33/12.8	2.6 (1.8,3.6)	5.6 (2.5,8.7)	3.1 (1.9,4.6)
Other	33.6	71/45.2	1.6 (1.2,2.0)	2.7 (1.0,4.5)	2.6 (1.9,3.4)
Not in ICCC*	45.7	5/2.4	2.1 (0.7,4.8)	4.7 (-3.3,12.8)	-

Abbreviations: SIR- standardized incidence ratio, AER-absolute excess risk, 95%CI- 95% confidence interval, ICCC-International Classification of Diseases.
*Not in ICCC- Survivors diagnosed before 1983 in Slovenia were classified in ICD7 and thus could not be converted to ICCC

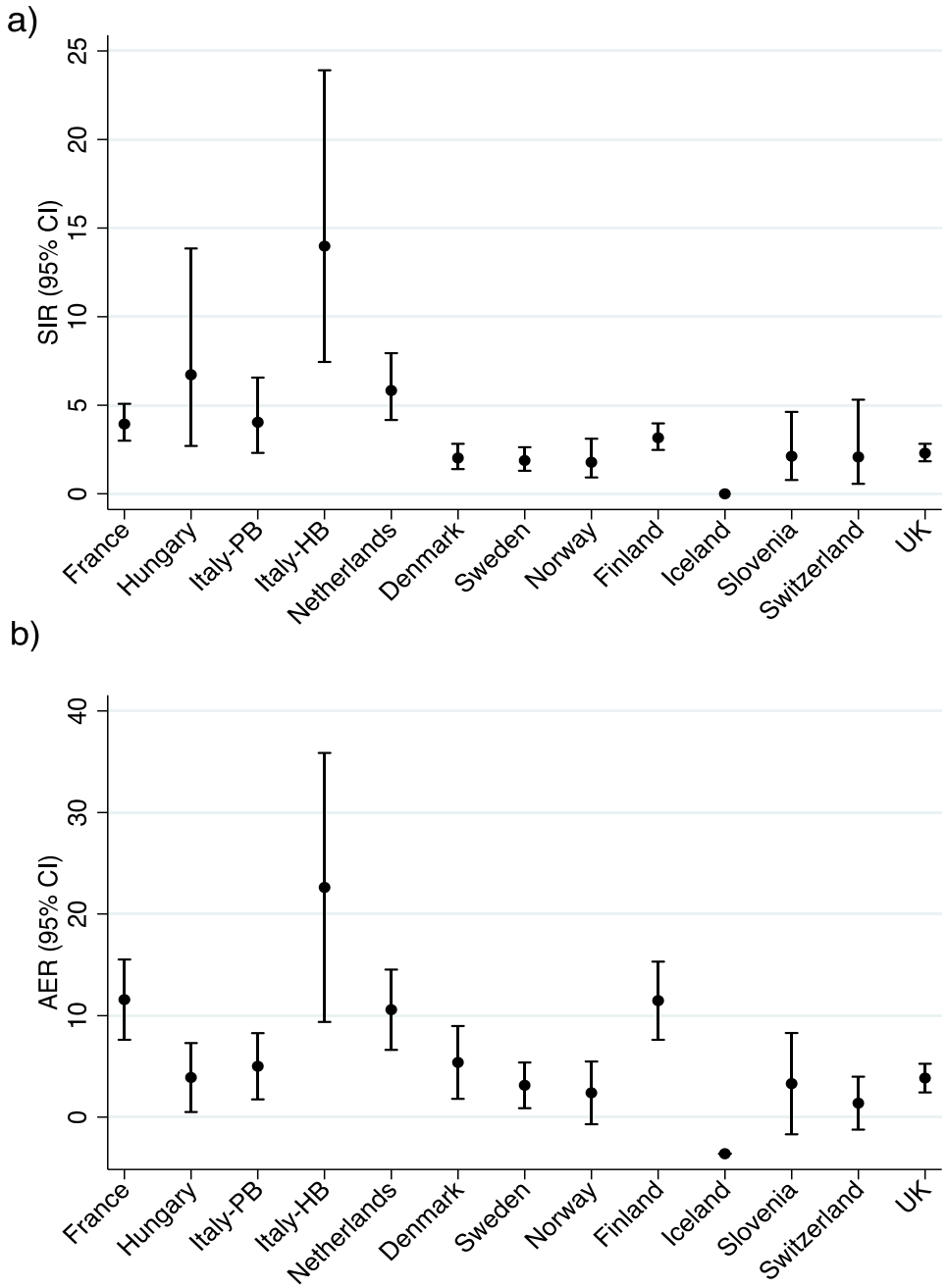


Figure 6.1: Risk of breast SPNs among childhood cancer survivors* stratified by country of diagnosis: a) Standardised Incidence ratios and b) Absolute excess risks

Abbreviations: SIR- standardized incidence ratio, AER- absolute excess risk, 95% CI- 95% confidence interval, PB- population based, HB- hospital based.
AERs are per 10,000 person-years
* Leukaemia survivors were not included in the French cohort; therefore leukaemia survivors were excluded when providing comparisons between countries. The observed number of breast SPNs among leukaemia survivors were 0 for Denmark, Norway, Iceland and Slovenia; 1 for Italy-HB and Italy-PB, 2 for Hungary, Sweden and Switzerland, 3 for Finland, 6 for UK and 7 for Netherlands

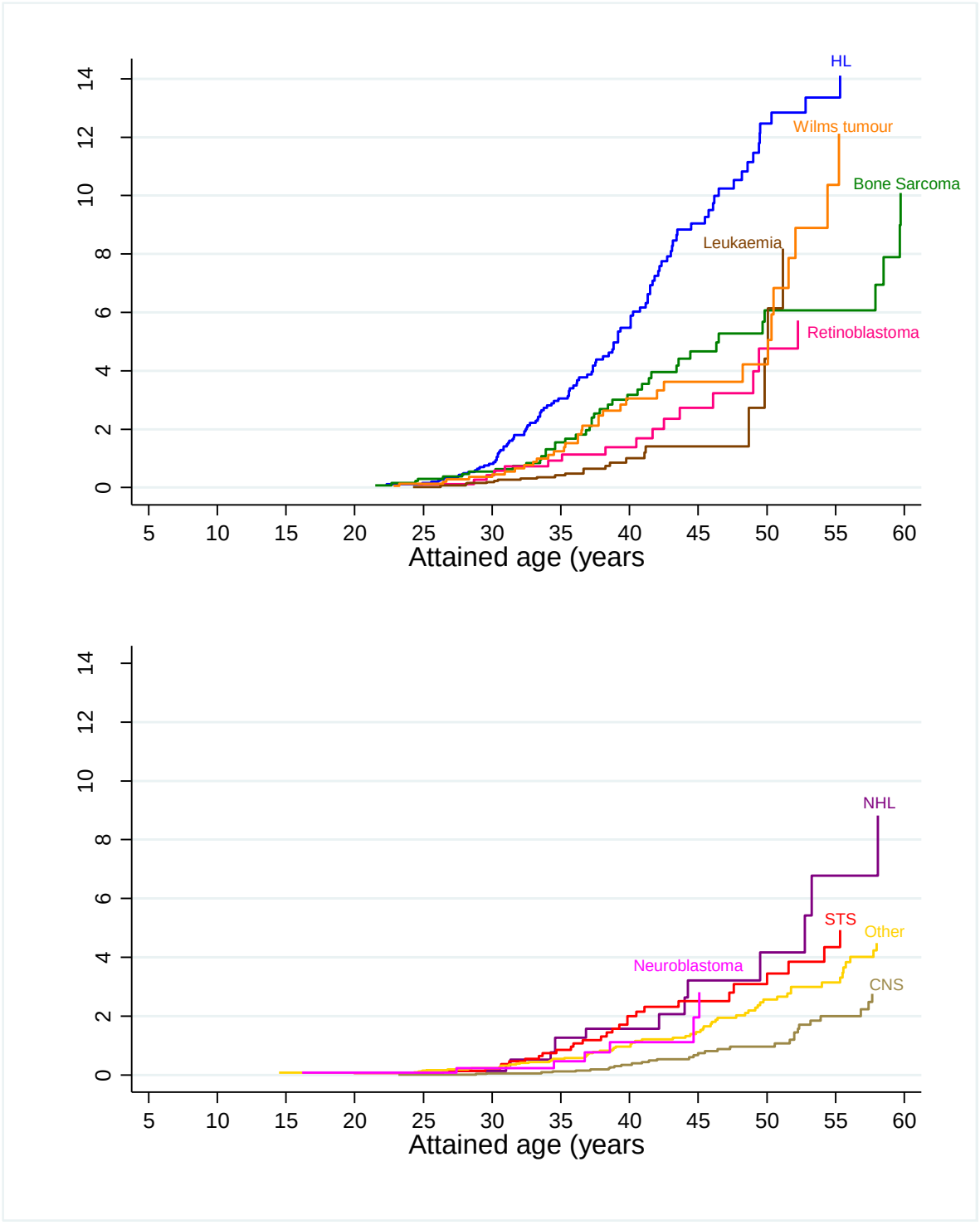


Figure 6.2: Cumulative incidence of breast SPNs stratified by childhood cancer type with attained age as time scale.

Table 6.4: Standardised incidence ratios, absolute excess risks, relative risks and relative excess risks stratified by country of diagnosis*

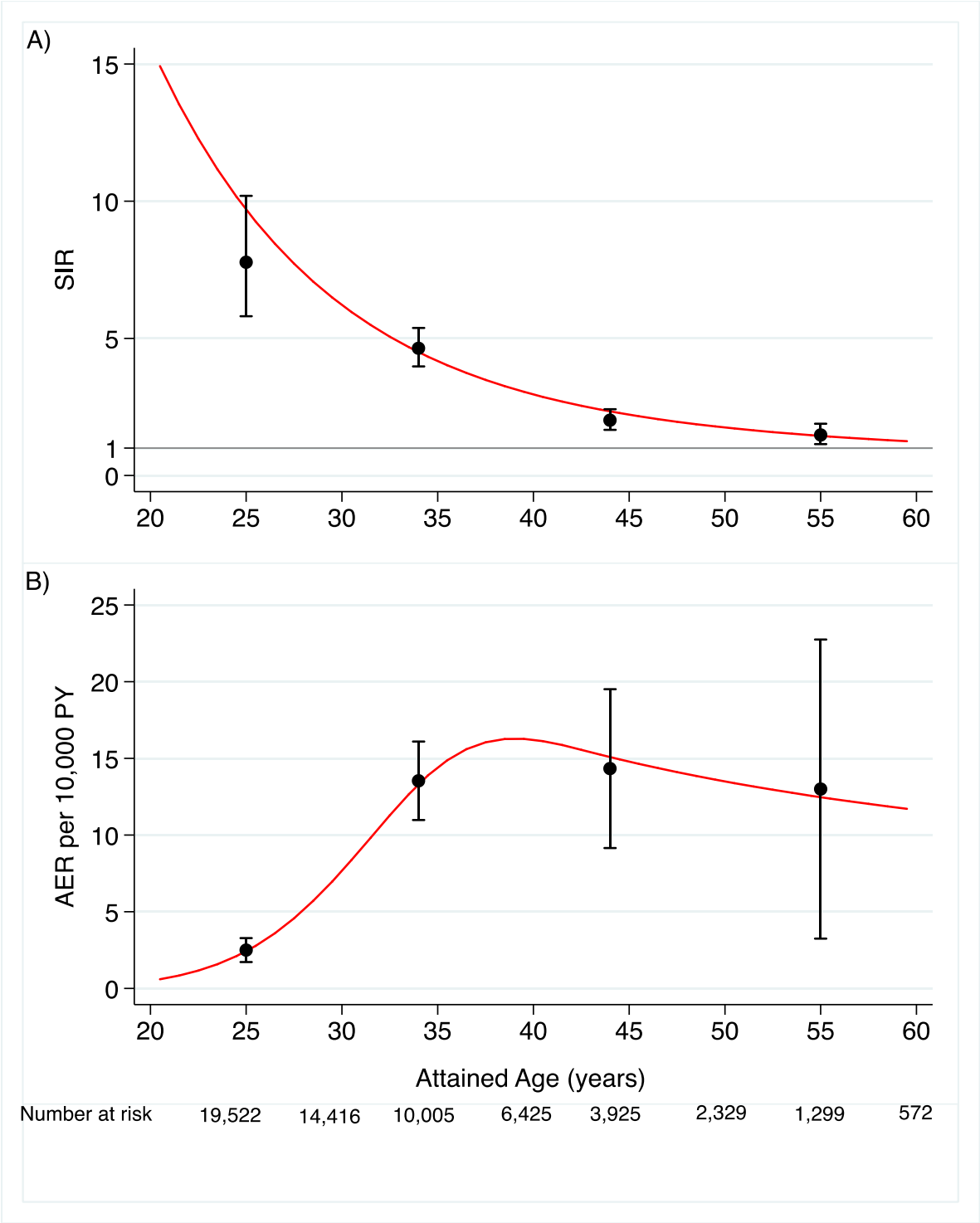
Country of Diagnosis	**O**	**SIR (95% CI)**	**RR (95%CI)†**	**AER (95% CI)**	**RER (95% CI) †**
France	59	3.9 (3.0,5.1)	1.6 (1.2,2.3)	11.6 (7.6,15.5)	2.2 (1.4,3.4)
Hungary	7	6.7 (2.7,13.8)	1.2 (0.6,2.7)	3.9 (0.5,7.3)	1.2 (0.5,3.2)
Italy-PB	16	4.0 (2.3,6.6)	0.9 (0.5,1.6)	5.0 (1.7,8.3)	0.9 (0.5,1.9)
Italy-HB	13	14.0 (7.4,23.9)	2.5 (1.4,4.6)	22.6 (9.4,35.9)	2.8 (1.5,5.5)
Netherlands	40	5.8 (4.2,7.9)	1.6 (1.0,2.3)	10.6 (6.6,14.5)	1.8 (1.1,3.0)
Denmark	34	2.0 (1.4,2.8)	1.3 (0.9,2.0)	5.4 (1.8,9.0)	1.0 (0.5,2.0)
Sweden	34	1.9 (1.3,2.6)	1.0 (0.7,1.6)	3.1 (0.9,5.4)	0.7 (0.4,1.4)
Norway	12	1.8 (0.9,3.1)	0.9 (0.5,1.6)	2.4 (-0.7,5.5)	0.6 (0.2,1.4)
Finland	73	3.2 (2.5,4.0)	1.8 (1.2,2.5)	11.5 (7.6,15.3)	1.4 (0.8,2.3)
Iceland	0	-	-	-	-
Slovenia	6	2.1 (0.8,4.6)	0.4 (0.1,3.1)	3.3 (-1.7,8.3)	0.4 (0.0-3.1)
Switzerland	4	2.1 (0.6,5.3)	0.4 (0.2,1.2)	1.4 (-1.2,4.0)	0.4 (0.1,1.2)
UK	89	2.3 (1.8,2.8)	Reference	3.8 (2.4,5.3)	Reference
$P_{heterogeneity}$			*<0.001*		*<0.001*

Abbreviations: SIR- standardized incidence ratio, AER- absolute excess risk, RR- relative risk, RER- relative excess risk, 95% CI- 95% confidence interval, PB-population based, HB- hospital based.

* Leukaemia survivors were not included in the French cohort; therefore leukaemia survivors were excluded when providing comparisons between countries. The observed number of breast SPNs among leukaemia survivors were 0 for Denmark, Norway, Iceland and Slovenia; 1 for Italy-HB and Italy-PB, 2 for Hungary, Sweden and Switzerland, 3 for Finland, 6 for UK and 7 for Netherland

†multivariable models were adjusted for age at diagnosis, decade of diagnosis, childhood cancer diagnosis and attained age (1-year age categories fitted as a restricted cubic spline).

Figure 6.3: Risk of breast SPNs among survivors of all childhood cancer expressed as a) standardized incidence ratios and b) absolute excess risks.



Abbreviations: SIR- Standardised Incidence Ratio, AER- absolute excess risk.
Smoothed estimate was calculated using a restricted cubic spline. Point estimates are for attained age groups: 20-29, 30-39, 40-49, 50+ and plotted at the median attained age value for each category.

Table 6.5: Standardised incidence ratios and absolute excess risks stratified by childhood cancer type and attained age.

Childhood Cancer	Median Attained Age	0-29 years			30-39 years			40+ years			Trend	
		O	SIR (95% CI)	AER (95% CI)	O	SIR (95% CI)	AER (95% CI)	O	SIR (95% CI)	AER (95% CI)	SIR P_{trend} †	AER P_{trend} †
Hodgkin Lymphoma	31.7	16	27.1 (15.5,44.0)	8.0 (3.9,12.1)	59	18.1 (13.8,23.4)	63.0 (46.0,80.1)	47	6.8 (5.0,9.0)	98.6 (65.5,131.7)	<0.001	<0.001
	*PYs**		*19198.2*			*8842.2*			*4060.9*			
Wilms tumour	27.8	5	9.3 (3.0,21.6)	1.2 (0.0,2.4)	20	7.1 (4.4,11.0)	24.9 (12.2,37.6)	12	2.5 (1.3,4.3)	25.9 (1.3,50.4)	0.020	<0.001
	PYs		*37198.9*			*6912.4*			*2766.0*			
Sarcoma	31.2	10	12.2 (5.8,22.4)	2.5 (0.8,4.1)	39	7.6 (5.4,10.5)	25.4 (16.2,34.5)	29	1.7 (1.2,2.5)	13.8 (2.0,25.5)	<0.001	<0.001
	PYs		*37291.6*			*13363.4*			*8954.1*			
Leukaemia	24.6	7	5.3 (2.1,11.0)	0.6 (0.1,1.2)	11	2.2 (1.1,4.0)	4.6 (-0.4,9.5)	6	1.9 (0.7,4.2)	14.3 (-9.5,38.1)	0.088	0.490
	PYs		*90872.0*			*13211.9*			*2017.4*			
Other	30.3	17	4.8 (2.8,7.7)	0.7 (0.3,1.2)	46	2.1 (1.6,2.8)	4.1 (1.9,6.4)	87	1.2 (1.0,1.5)	4.4 (-0.3,9.0)	<0.001	0.004
	PYs		*181951.9*			*59067.2*			*39175.8*			

Abbreviations: SIR-standardised incidence ratio, AER-absolute excess risk, 95% CI- 95% confidence interval, PYs- person-years at risk

†models for trend were adjusted for decade of treatment, age at diagnosis and attained age.

* Person-years at risk shown in grey for each attained age strata.

Table 6.6: Relative risks and relative excess risks by decade of childhood cancer diagnosis

		O	RR (95%CI)*	RER (95%CI)*
All Childhood Cancer	<1970	165	0.9 (0.7,1.2)	0.7 (0.5,1.0)
	1970-1979	136	Reference	Reference
	1980-1989	83	1.0 (0.8,1.4)	0.9 (0.7,1.4)
	≥1990	27	1.3 (0.8,2.0)	1.1 (0.6,1.9)
	P_{trend}		*0.152*	*0.119*
Hodgkin lymphoma	<1970	27	0.7 (0.4,1.2)	0.7 (0.4,1.2)
	1970-1979	52	Reference	Reference
	1980-1989	29	0.7 (0.4,1.2)	0.7 (0.4,1.2)
	≥1990	14	1.0 (0.5,2.1)	0.9 (0.4,2.0)
	P_{trend}		*0.837*	*0.759*
Wilms tumour	<1970	19	1.1 (0.5,2.7)	1.2 (0.4,3.9)
	1970-1979	10	Reference	Reference
	1980-1989	7	2.4 (0.8,6.8)	4.0 (1.2,13.4)
	≥1990	1	7.8 (0.7,82.0)	14.4 (1.0,199.5)
	P_{trend}		*0.268*	*0.113*
Sarcoma	<1970	26	0.7 (0.4,1.3)	0.5 (0.2,1.3)
	1970-1979	25	Reference	Reference
	1980-1989	22	1.3 (0.7, 2.4)	1.3 (0.7,2.8)
	≥1990	5	1.4 (0.4, 4.2)	1.5 (0.5,5.1)
	P_{trend}		*0.109*	*0.059*
Leukaemia	<1970	2	0.6 (0.1,4.1)	.
	1970-1979	12	Reference	Reference
	1980-1989	6	0.8 (0.3,2.5)	0.9 (0.1,6.3)
	≥1990	4	2.8 (0.5,14.4)	4.0 (0.4,40.0)
	P_{trend}		*0.324*	*0.194*

Abbreviations: RR- relative risk, RER-relative excess risk, 95%CI-95% confidence interval

* Adjusting for country, age at diagnosis, childhood cancer type (overall only) and attained age (1-year age categories fitted as a restricted cubic spline).

Chapter 7

Discussion and Summary of Thesis

7.1 PRINCIPAL FINDINGS

The cohort study presented in Chapter 2 of this thesis quantified the risk of specific SPNs after each of 17 types of TYA cancer. Overall, 12,321 SPNs were diagnosed in 11,565 survivors; most frequently among survivors of breast cancer, cervical cancer, testicular cancer, and Hodgkin lymphoma. Among these survivors, the excess number of SPNs observed increased with increasing years from diagnosis for all SPNs combined and for SPNs at each specific anatomical site which would have been directly irradiated if radiotherapy had been used to treat the TYA cancer. Beyond 30 years from diagnosis the percentage of excess numbers of SPNs was at greatest risk at such directly irradiated sites or at sites of likely smoking-related cancers (lung cancer). Beyond 30 years from diagnosis, lung cancer accounted for 45% of the excess number of SPNs after breast cancer in women; lung, colorectal, and bladder cancers accounted for 82% of the excess number of SPNs after cervical cancer; prostate, bladder, colorectal and lung cancer accounted for 61% of the excess number of SPNs after testicular cancer; breast and lung cancer accounted for 58% of the excess number of SPNs after Hodgkin lymphoma in women; lung cancer accounted for 41% of the excess number of SPNs after Hodgkin lymphoma in men. Age at diagnosis/treatment was not an important risk factor for the development of SPNs, except for breast cancer after Hodgkin lymphoma in women. Chapter 2 provides risk estimates that are a considerable advance on previous knowledge and provide an initial basis for developing evidence-based long-term clinical follow-up guidelines for TYA cancer survivors in relation to SPNs. No such guidelines currently exist.

Chapter 3 reported on the risks of hospitalisation for specific cerebrovascular events among TYA cancer survivors by linking the TYACSS cohort to the HES database (England only).

Overall, 2,782 cancer survivors were hospitalised for a cerebrovascular event, which was 40% higher than expected (SHR=1.4, CI=1.3-1.4). With regards to types of cerebrovascular event, TYA cancer survivors were at 2-fold, 1.5-fold and 1.4-fold increased risk of a cerebral haemorrhage, cerebral infarction and `other cerebrovascular event`, respectively. Survivors of CNS tumours (SHR=4.6, CI=4.3-5.0), head & neck tumours (SHR=2.6, CI=2.2-3.1) and leukaemia (SHR=2.5, CI=1.9-3.1) were at greatest risk. By age 60 years, 9%, 6%, and 5% of CNS tumour, head & neck tumour, and leukaemia survivors, respectively, had been hospitalised for a cerebrovascular event. Of particular concern was the number of excess cerebral infarctions among CNS tumour survivors beyond age 60 years and head & neck tumour survivors at any age. Beyond age 60, every year 0.4% of CNS tumour survivors were hospitalised for a cerebral infarction (versus 0.1% expected). Whereas at any age, every year 0.2% of head & neck tumour survivors were hospitalised for a cerebral infarction (versus 0.06% expected). The findings from Chapter 3 suggest that survivors of CNS tumours, head & neck tumours, and leukaemia, should be considered for surveillance and counselling in relation to cerebrovascular risk factors, and further studies are needed to investigate the potential impact of pharmacological interventions for cerebral infarction prevention.

Chapter 4 reported the risk of premature mortality among survivors of TYA CNS tumours by linking the TYACSS cohort to the national death registers. Overall 4,099 deaths were observed which was 7-fold that expected (SMR=6.6, CI=6.4-6.8). Beyond 25 years from diagnosis the majority of the excess deaths were attributable to non-neoplastic causes for survivors of gliomas (59%), craniopharyngioma (82%), other pituitary tumours (89%) and ependymoma (58%). Whereas beyond 25 years from diagnosis the majority of the excess deaths were attributable to neoplastic causes for survivors of meningioma (79%) and

embryonal tumours (56%). Of particular concern was the increased mortality due to strokes in long-term survivors of glial and pituitary tumours; as well as the increased mortality due to cardiac diseases in long-term survivors of other pituitary tumours. Among glial tumour survivors, strokes contributed 30% of the total AER beyond 25 years from diagnosis. Among other pituitary tumour survivors, strokes and cardiac disease contributed 25% and 21%, respectively, of the total AER beyond 25 years from diagnosis. In contrast to deaths due to neoplastic causes the excess of non-neoplastic deaths might be preventable with appropriate clinical surveillance and interventions. The general conclusion is that focus should be on prevention of long-term deaths from non-neoplastic causes among CNS tumour survivors, especially stroke and cardiac deaths among glial and other pituitary tumour survivors.

Chapter 5 reports the first of two investigations in this thesis to utilise the PanCareSurFup cohort. The risk of subsequent soft-tissue sarcoma among childhood cancer survivors was investigated. Overall, 301 soft-tissue sarcoma were observed, which was 16-fold that expected (CI=14–18). With regards to specific types of soft-tissue sarcoma, highest SIRs were observed for malignant peripheral nerve sheath tumours (SIR=41, CI=14–18), leiomyosarcoma (SIR=30, CI=24–37), and fibromatous neoplasms (SIR=12, CI=9–16). In recent decades (1980s onwards), treatment for good prognosis childhood cancer has involved smaller radiation fields and reduced cumulative doses than in earlier decades, however among survivors in the PanCareSurFup cohort the excess risk of soft-tissue sarcoma overall and for specific soft-tissue sarcoma subtypes did not decrease from <1970 to 1990-2008. With regards to the AER, the number of excess fibromatous neoplasms and malignant peripheral nerve sheath tumours remained constantly low across all years from diagnosis and at all attained ages at less than 1 per 10,000 survivors per year. In contrast the number of excess

leiomyosarcomas increased with increasing years from diagnosis and attained age; especially among retinoblastoma survivors, for whom beyond 45 years from diagnosis there were 53 excess leiomyosarcomas observed per 10,000 survivors per year. This study provides evidence that clinical follow-up guidelines should recommend long-term surveillance for leiomyosarcoma among retinoblastoma survivors. In contrast, there is no evidence to suggest long-term surveillance for fibromatous neoplasms or malignant peripheral nerve sheath tumours among childhood cancer survivors is warranted.

Chapter 6 reports the second of two investigations in this thesis to utilise the PanCareSurFup cohort. The risk of breast SPNs experienced by survivors of childhood and adolescent cancer was investigated, particularly among long-term survivors (>40 years of age). The International Guideline Harmonisation Group (IGHG) consortium strongly recommends breast surveillance in the form of annual mammography between the ages of 15-50 years for female childhood cancer survivors treated with high-dose chest radiotherapy (≥20 Gy). However, there is a lack of empirical evidence to establish if this high level of surveillance should also be recommended for survivors after age 50 years[58]. In addition, current IGHG recommendations for breast cancer surveillance of individuals aged 40-50 years are based on evidence provided from studies with small number of person-years and few breast cancers observed after age 40 years, particularly for specific childhood cancers. Chapter 6 within this thesis provides evidence that childhood cancer survivors remain at increased risk of breast SPNs beyond age 50 years. Furthermore, Hodgkin lymphoma, Wilms tumour and sarcoma survivors had substantially increased excess numbers of breast SPNs beyond age 40 years with 99, 26 and 14 excess breast SPNs per 10,000 survivors per year, respectively. Our study provides evidence that should aid revising and updating of the current breast cancer

surveillance guidelines for female survivors of childhood cancer. However, observational studies, such as case-control studies including detailed information on the regimen and fractionation of radiotherapy to the chest and cumulative chemotherapy exposures (doses of each chemotherapeutic drug) among this ageing cancer survivor population are needed to provide more robust evidence. Such studies currently exist, however the number of ageing survivors diagnosed as children included in most, if not all, such studies is small[55, 57].

7.2 STRENGTHS AND LIMITATIONS OF RESEARCH

Chapters 2-4 in this thesis are based on the largest ever population-based cohort study (TYACSS) of long-term adverse health outcomes among TYA cancer survivors worldwide. A major strength of the TYACSS is its population-based design and large size with over 200,000 5-year survivors of TYA cancer, this enables unprecedentedly reliable estimates of excess risks of adverse health outcomes to be quantified. A principal advantage of population-based studies over hospital or treatment centre (non-population based studies) studies is that they are less likely to be subject to selection bias [227]. Selection bias can occur when the study population is not representative of the eligible population[228] (e.g. all TYA cancer survivors). For example in treatment centre based cohorts, the study population is often ascertained from the hospital in which the cancer survivor received treatment, therefore the study population is likely to be younger than the eligible population because the long-term clinical follow-up of patients tends to decrease with age as older patients are more likely to be "lost to follow-up"; in addition the study population may not include all diagnostic types of cancer. This may result in any risk estimates produced not being generalisable to the full eligible population[228].

Another strength of the TYACSS is the ability to undertake electronic record linkage of the cohort to the national death register, national cancer register and the HES database. This enables a complete spectrum of fatal and non-fatal adverse health outcomes to be investigated in all survivors of TYA cancer in England and Wales in a relatively easy and inexpensive manner. Such linkage opportunities with electronic health databases currently only exist in very few countries. Furthermore, unlike studies which rely on (self-reported) questionnaire data, this methodology is not susceptible to recall or non-responder bias [227].

Nonetheless, the TYACSS is also subject to some limitations. Pathological reports to provide confirmation of SPNs were not available for the study in Chapter 2, which estimated the excess risk of SPNs in the TYACSS cohort. Pathology reports are a way to confirm whether the information provided on cancer registrations is accurate and distinguish recurrence/relapse/metastatic spread of the original primary tumour from subsequent primary tumours. To ensure that the excess risk of SPNs was not an overestimate, a conservative method (IACR/IARC rules and exclusion of same site tumours) was implemented to distinguish between a SPN and a recurrence/relapse/metastatic spread of the original TYA cancer. Therefore the risk estimates provided in Chapter 2 were likely to underestimate the true risk of developing a SPN within TYA survivors.

Chapter 5 and 6 of this thesis are based on the largest cohort in the world ever assembled to investigate the risk of SPNs among childhood cancer survivors. Previous cohort studies of childhood and adolescent cancer survivors within individual countries had insufficient numbers of survivors aged over 40 years to satisfactorily address the risks of developing a SPN among older survivors[96, 98, 100, 102, 104, 106]. The major strength of PanCareSurFup is that

the pooled cohort of childhood and adolescent cancer survivors from 13 European countries provides a large number of survivors with very long follow-up and thus enables reliable estimates of long-term risks of SPNs to be quantified. Another advantage of the large size of the cohort and long follow-up was that reliable risk estimates stratified by numerous potential explanatory factors could be quantified (e.g. specific morphological types of soft-tissue sarcoma), which was previously not possible.

Another strength of the PanCareSurFup study is that several contributing countries have a long history of population-based cancer registrations dating as far back as the 1940s, therefore for the first time, risk estimates based on large number of SPNs and person-years beyond age 40 years were produced. Many of the cohorts in PanCareSurFup (see Table 5.1) ascertained SPNs through linkage with population-based cancer registries. This has several advantages over the North American Childhood Cancer Survivor Study (CCSS), a non-population-based cohort study of 34,033 survivors of childhood cancer that may be susceptible to selection bias as described above [99].

A potential limitation of the PanCareSurFup cohort is the significant heterogeneity in excess risk between contributing cohorts particularly between population-based and hospital-based cohorts (treatment centres). This is more than likely due to differences in treatment prescribing in the treatment centre based cohorts, which are often international referral centres for relapsed/recurrent cancers and therefore disproportionately include higher levels of treatment exposures. When sensitivity analyses were conducted excluding treatment centre based cohorts for both studies in Chapters 5 and 6, the overall estimates of excess risk did not

change appreciably across remaining cohorts, indicating that the heterogeneity in excess risk is partially attributable to the treatment centre based cohorts.

A limitation of both the TYACSS and PanCareSurFup study is the lack of available information on: cumulative exposures, types and doses of specific chemotherapy drugs; cumulative exposures and fractionation of radiotherapy; and details of any genetic condition that may affect the excess risk of adverse health outcomes. To obtain this information, medical records for each of the 200,945 TYA cancer survivors and 69,460 childhood cancer survivors would need to be obtained. As a large proportion of the PanCareSurFup cohort and the entire TYACSS cohort are obtained from population-based cancer registries, this information is not readily available and it would not be practically feasible to collect this information for the large numbers of survivors included in both cohorts. To overcome this limitation, nested case-controls studies could be conducted. This would involve selecting cases (survivors with the outcome of interest- e.g. soft-tissue sarcoma SPN) and matched controls (survivors without the outcome of interest) from the underlying cohorts. Although it would still be a research intensive and labour-some process to obtain medical records for nested case-control studies; this would be a much more manageable task than obtaining this information for the full PanCareSurFup and TYACSS cohorts. As part of the PanCareSurFup study, nested case-control studies are currently being conducted to investigate the dose-response relationship between cumulative dose of radiation from radiotherapy, cumulative dose of specific chemotherapy drugs, existing genetic conditions, and the risk of the following adverse health outcomes: subsequent soft-tissue sarcoma, subsequent bone sarcoma, subsequent genitourinary neoplasms, subsequent digestive neoplasms and cardiac disease.

Therefore, limitations of the studies included in this thesis are already starting to be addressed with further studies.

Another limitation of all the studies presented in this thesis was that information on modifiable lifestyle factors such as diet, smoking, alcohol, exercise and obesity, or comorbidities such as diabetes and hypertension that may also contribute to the excess risk of adverse health outcomes were not available. At present, outside of case-control studies it is difficult to overcome this limitation. There are plans for linkage with GP prescriptions and also with supermarket consumption, but this is not yet fully available.

7.3 RECOMMENDATIONS FOR FUTURE RESEARCH

It is not possible or necessary for every cancer survivor to be on regular long-term clinical follow-up of adverse health outcomes, therefore it is important to risk-stratify cancer survivors so that appropriate recommendations on clinical follow-up can be advised. Risk stratification is a process whereby cancer survivors are grouped based on their previous treatment exposures and after other risk factors including genetic predisposition (e.g. RB1, BRCA1/2, and NF1/2), and then stratified in relation to anticipated risk. Studies such as those presented in this thesis can be used to provide a basis for risk stratifying cancer survivors; however evidence-based guidelines always require further studies to provide the most appropriate recommendation possible. Thus there is a need to build in regular updates into guidelines as evidence accumulates.

Currently individuals in the general population who at high risk of having a stroke (e.g. individuals with hypertension or high blood pressure) are recommended to receive

pharmacological interventions to reduce the risk of cerebral infarction [180, 181]. Currently there are no pharmacological interventions offered to TYA cancer survivors at high risk of cerebral infarction thus future studies should investigate the potential impact of pharmacological interventions for cerebral infarction prevention among survivors of CNS tumour, head & neck tumours and leukaemia.

Future studies should take advantage of the existing national population-based electronic health databases, such as HES, the Patient Episode Database for Wales (PEDW)[229], and the National Institute for Cardiovascular Outcomes Research (NICOR) databases[230]. PEDW database contains information on hospitalisations to hospitals in Wales, and is similar to the HES database [229]. The NICOR collects information from hospitals on individuals who have cardiovascular diseases. These electronic databases provide an easy and efficient method of analysing adverse health outcomes.

In Chapters 2 through 4, information on exposures to cancer treatment (chemotherapy drugs and doses, radiotherapy regimens and fractions) was not available; therefore studies are needed in which cumulative exposures of treatment are investigated. As stated above, this could be achieved through nested case-control studies. A problem often encountered with retrospective cohorts is that information on treatments obtained from medical notes has been destroyed or are very difficult to obtain (time-consuming and expensive). In recent years, several national standards have been produced which requires the collection and recording of treatment exposures among cancer patients in England. In 2012, the collection of all systemic anti-cancer therapy including chemotherapy in English NHS hospitals was launched and recording of this data became mandatory for all NHS trusts in 2014, the data collected forms

the Systemic Anti-Cancer Therapy (SACT) dataset [231]. Since 2009, all NHS providers of radiotherapy services are required to record information on all radiotherapy given and this is recorded in the National Radiotherapy Dataset (RTDS) [232]. In the future these datasets could be used to make available, for research purposes, treatment exposures from cancer survivors treated in more recent diagnostic periods. For example, a prospective cohort study of cancer survivors could be conducted where all treatment information for the cancer is obtained from the SACT and RTDS datasets. This will enable treatment risk factors for adverse health outcomes to be quantified without the problems of retrospective treatment data collection.

In chapter 5, the risks of STS SPNs among the PanCareSurFup cohort were reported, however as mentioned in the previous section, information to investigate the association of treatment exposures and excess risk of STS SPNs was not available. To overcome this limitation, a nested case-control study is required. As previously mentioned as part of the PanCareSurFup objectives, a nested case-control study is currently on-going as part of one of the PanCareSuFup objectives. Information on the cumulative exposure to chemotherapy and radiotherapy, and underlying genetic conditions of childhood cancer survivors in the study has currently been collected. The next stage is to perform radiation dosimetry so that the exact radiation dose to the site where the tumour developed can be determined. This enables the relationship of the excess risk of STS and dose of radiotherapy to be investigated.

In chapter 6, the risks of breast SPNs among the PanCareSurFup were reported with a particular focus on survivors over age 40 years. A major risk factor for breast SPNs is previous exposure to chest irradiation (including any high-dose radiotherapy that has the chest in the field). IGHG requires additional evidence to support a guideline for the continued

surveillance of childhood cancer survivors beyond age 50 years who were treated with chest radiotherapy, thus more observational studies including detailed information on cumulative doses of irradiation to the chest and cumulative chemotherapy exposures among this ageing cancer survivor population are needed to provide more conclusive evidence.

7.4 OVERALL CONCLUSION

This thesis aimed to investigate the risk of adverse health outcomes among two populations of long-term survivors of childhood, teenage and young adult cancers. The thesis provides evidence to help risk stratify childhood, teenage and young adult cancer survivors according to their risk of specific adverse health outcomes, and thus identifies survivors who would benefit from long-term clinical surveillance. In particular the studies presented in this thesis provide an evidence base for updating existing and producing new guidelines and recommendations for the long-term surveillance of adverse health outcomes in childhood, teenage and young adult cancer survivors.

Chapter 8

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APPENDICES

APPENDIX 1 – Copyright Agreement from Karger Publishers for Figures 1.1, 1.2 and 1.3, and Table 1.1.

APPENDIX 2 – Classification scheme for tumours diagnosed in adolescents and young adults[13]

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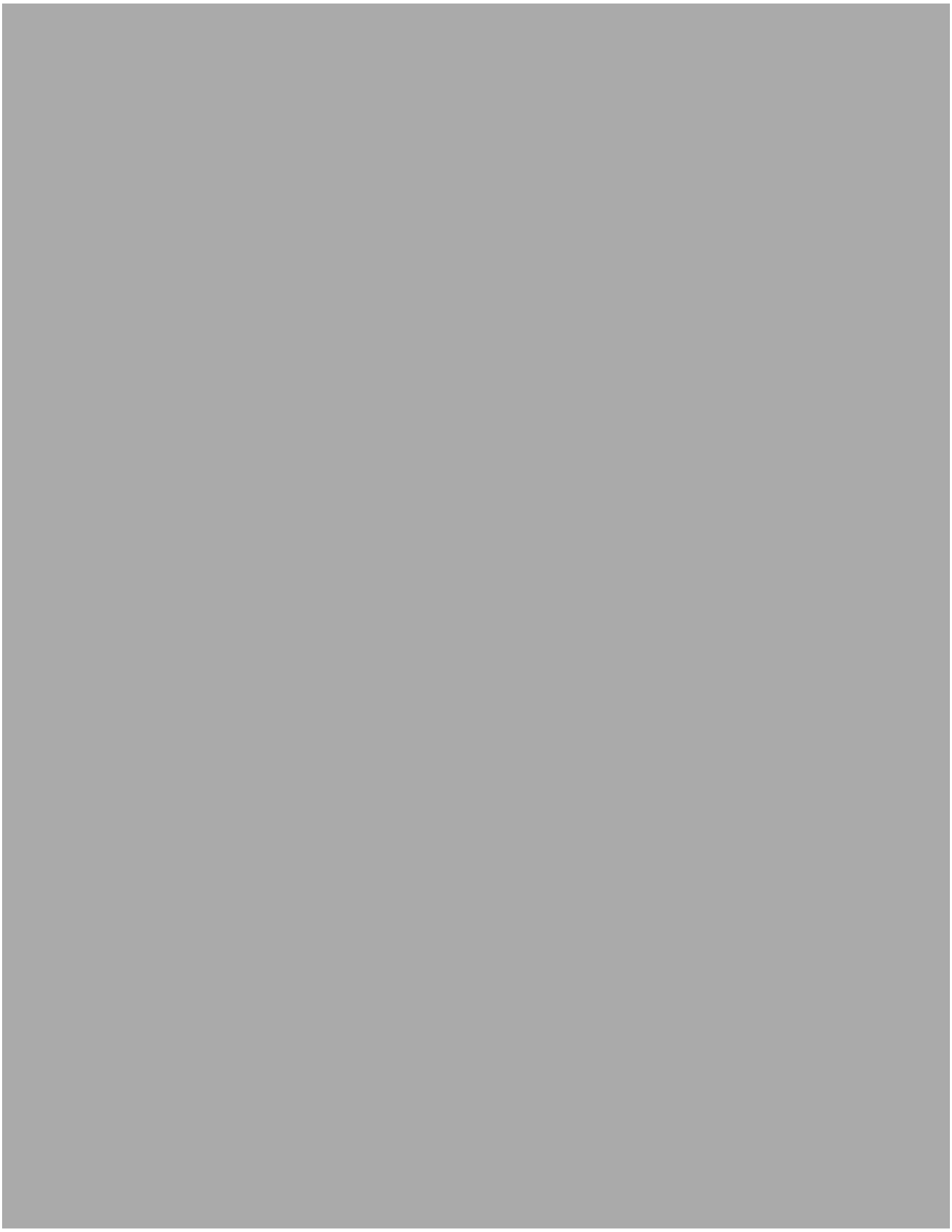

APPENDIX 2 – Classification scheme for tumours diagnosed in adolescents and young adults[13]

Diagnostic group		ICD-02	
		Morphology code	Topography code restrictions
1.	LEUKEMIAS		
1.1	Acute lymphoid leukemia	9821, 9825, 9826, 9827	
1.2	Acute myeloid leukemia	9840, 9861, 9866, 9891, 9910, 9942	
1.3	Chronic myeloid leukemia	9863	
1.4	Other and unspecified leukemias		
1.4.1	Other lymphoid leukemia and lymphoid leukaemia, NOS	9820,9822,9823,9824	
1.4.2	Other myeloid leukemia and myeloid leukaemia, NOS	9860,9862,9864,9865	
1.4.3	Other specified leukemias	9810, 9830, 9841, 9842, 9850, 9867, 9868, 9870, 9880, 9890, 9892, 9893, 9894, 9900, 9920, 9930, 9931, 9932, 9940, 9941	
1.4.4	Unspecified leukemias	9800-9804	
2.1	LYMPHOMAS		
2.1.1	NHL, specified subtype	9593-9649, 9670-9714, 9723	
2.1.2	Unspecified NHL	9590, 9591, 9592	
2.2	Hodgkin disease:		
2.2.1	Hodgkin disease, specified subtype	9652-9667	
2.2.2	Hodgkin disease, NOS	9650	
3.	CNS AND OTHER INTRACRANIAL AND INTRASPINAL NEOPLASMS (tumors with any behavior code were included)		
3.1	Astrocytoma		
3.1.1	Specified low-grade astrocytic tumors	9380	C72.3
		9410-9424	None
3.1.2	Glioblastoma and anaplastic astrocytoma	9401, 9440-9442, 9481	None
3.1.3	Astrocytoma, NOS	9400	None
3.2	Other glioma	9380	Except C72.3
		9381-9384, 9430, 9443-9460	None
3.3	Ependymoma	9391-9394	None
3.4	Medulloblastoma and other PNET		
3.4.1	Medulloblastoma	9470-9473	C71.6
3.4.2	Supratentorial PNET	9470-9473	Except C71.6
3.5	Other specified intracranial and intraspinal neoplasms	8140, 8270-8281, 8300, 9161, 9350, 9360-9362, 9390, 9480, 9505, 9530-9539, 9540-9570	Except C70.0–C72.9 C75.1, C75.3
3.6	Unspecified intracranial and intraspinal neoplasms		
3.6.1	Unspecified malignant intracranial and intraspinal neoplasms (behavior code of 3 or more)	8000-8004, 9990	C70.0-C72.9, C75.1, C75.3
3.6.2	Unspecified benign and borderline intracranial and intraspinal neoplasms (behavior code of less than 3)	8000-8004, 9990	C70.0-C72.9, C75.1, C75.3
4.	OSSEOUS AND CHONDROMATOUS NEOPLASMS, EWING TUMOR, AND OTHER NEOPLASMS OF BONE		
4.1	Osteosarcoma	9180-9190	None
4.2	Chondrosarcoma	9220-9240	None
4.3	Ewing tumor	9260, 9364[b]	None[c]
4.4	Other specified and unspecified bone tumors		
4.4.1	Other specified bone tumors	8812, 9250, 9261, 9370	None
4.4.2	Unspecified bone tumors	8000-8004, 8800, 8801, 8803	C40.0-C41.9
5.	SOFT TISSUE SARCOMAS		
5.1	Fibromatous neoplasms	8810, 8811, 8813-8833	None
5.2	Rhabdomyosarcoma	8900-8920, 8991	None
5.3	Other specified soft tissue sarcoma:		
5.3.1	Specified	8804, 8840-8896, 8990, 9040-9044, 9120-9150, 9170, 9251, 9561,9581, 9580	None[d]
		9540,9560	Except C70.0–C72.9, C75.1, C75.3
5.3.2	Unspecified	8800-8803	Except C40.0–C41.9
6.	GERM CELL AND TROPHOBLASTIC NEOPLASMS		
6.1	Germ cell and trophoblastic neoplasms of gonads.	9060-9102	C56.9, C62.0–C62.9
6.2	Germ cell and trophoblastic neoplasms of nongonadal sites		
6.2.1	Intracranial (tumors with any behavior code are included)	9060-9102	C70.0-C72.9, C75.1, C75.3

(continued)

Diagnostic group		ICD-02	
		Morphology code	Topography code restrictions
6.2.2	Other nongonadal sites	9060-9102	Any site except C56.9, C62.0–C62.9, C70.0–C72.9, C75.1, C75.3
7.	MELANOMA AND SKIN CARCINOMAS		
7.1	Melanoma	8720-8780	None
7.2	Skin carcinomas	8010-8580	C44.0–C44.9
8.	CARCINOMAS		
8.1	Thyroid carcinoma	8010-8580	C73.9
8.2	Other carcinoma of head and neck		
8.2.1	Nasopharyngeal carcinoma	8010-8580	C11.0–C11.9
8.2.2	Other sites in lip, oral cavity and pharynx.	8010-8580	C00.0–C10.9, C12.0–C14.8
8.2.3	Nasal cavity, middle ear, sinuses, larynx, and other and ill-defined head and neck	8010-8580	C30.0–C32.9, C76.0
8.3	Carcinoma of trachea, bronchus, and lung	8010-8580	C33.0–C34.9
8.4	Carcinoma of breast	8010-8580	C50.0–C50.9
8.5	Carcinoma of genitourinary tract:		
8.5.1	Carcinoma of kidney	8010-8580	C64.9
8.5.2	Carcinoma of bladder	8010-8580	C67.0–C67.9
8.5.3	Carcinoma of gonads	8010-8580	C56.0, C62.0–C62.9
8.5.4	Carcinoma of cervix and uterus	8010-8580	C53.0–C55.9
8.5.5	Carcinoma of other and ill-defined sites in genitourinary tract	8010-8580	C51.0–C52.9, C57.0–C57.9, C60.0–C61.9, C63.0–C63.9, C65.9, C66.9, C68.0–C68.9
8.6	Carcinoma of gastrointestinal tract		
8.6.1	Carcinoma of colon and rectum	8010-8580	C18.0–C21.8
8.6.2	Carcinoma of stomach	8010-8580	C16.0–C16.9
8.6.3	Carcinoma of liver and intrahepatic bile ducts	8010-8580	C22.0, C22.1
8.6.4	Carcinoma of pancreas	8010-8580	C25.0–C25.9
8.6.5	Carcinoma of other and ill-defined sites in gastrointestinal tract	8010-8580	C15.0–C15.9, C17.0–C17.9, C23.0–C24.9, C26.0–C26.9
8.7	Carcinoma of other and ill-defined sites, NEC		
8.7.1	Adrenocortical carcinoma	8010-8580	C74.0–C74.9
8.7.2	Carcinoma of other and ill-defined sites, NEC	8010-8580	Any other C codes including C58.9 except C70.0–C72.9, C75.1, C75.3
9.	MISCELLANEOUS SPECIFIED NEOPLASMS, NEC		
9.1	Other pediatric and embryonal tumors, NEC:		
9.1.1	Wilms tumor	8960-8962	
9.1.2	Neuroblastoma	9490, 9500	
9.1.3	Other pediatric and embryonal tumors, NEC	8963, 8964, 8970-8972, 8981, 9501-9523	
9.2	Other specified neoplasms, NEC		
9.2.1	Paraganglioma and glomus tumors	8680-8710	
9.2.2	Other specified gonadal tumors	8600-8650, 9000	
9.2.3	Myeloma, mast cell tumors, and miscellaneous lymphoreticular neoplasms, NEC	9720-9764	
9.2.4	Other specified neoplasms, NEC	8930-8951, 8980, 9020, 9050-9053, 9110, 9270-9330	
10.	UNSPECIFIED MALIGNANT NEOPLASMS, NEC		
10.	Unspecified malignant neoplasms, NEC	8000-8004,9990	Any site except: C40.0–C41.9, C70.0–C72.9, C75.1, C75.3

ICD-O2: International Classification of Diseases for Oncology, 2nd edition; NOS: not otherwise specified; NHL: non-Hodgkin lymphoma; CNS: central nervous system; PNET: primitive neuroectodermal tumor; NEC: not elsewhere classified.

[a] Unless otherwise specified, only tumors with behavior codes of 3 or more were included.

[b] Included peripheral neuroectodermal tumors.

[c] Includes Ewing tumor and peripheral neuroectodermal tumors coded to extraskeletal sites.

[d] Includes malignant fibrous histiocytoma of the bone.

APPENDIX 3 – International Classification for Childhood Cancers (ICCC)[79]

Diagnostic group	ICD-O-3 code(s)[10] 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)

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)

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.