Epidemiological Analysis of Survivorship after Childhood Cancer

by

Kwok Fai Wong

A thesis submitted to
The University of Birmingham
for the degree of
Doctor of Philosophy

Institute of Applied Health Research
The University of Birmingham
February 2016

Abstract

This thesis investigates the adverse outcomes amongst survivors of childhood cancer using the British Childhood Cancer Survivor Study (BCCSS) and the Pancare Childhood and Adolescent Cancer Survivor Care and Follow-up studies (PCSF).

The specific aims were to investigate (1) adverse outcomes up to 50 years of follow-up in survivors of Wilms' tumour; (2) risks of hospitalisations due to renal morbidities in childhood cancer survivors; (3) risk of subsequent primary neoplasms arising in the digestive system in survivors of childhood cancer; and (4) adverse outcomes beyond 50 years of follow-up in survivors of heritable retinoblastoma.

This thesis demonstrated that survivors of Wilms' tumour are at substantial risk of premature mortality, particularly for those who have survived 30 years from original diagnosis. This particular group of survivors have the highest risk of hospitalisations due to renal morbidities, such as chronic renal failure, and subsequent primary neoplasms in specific organs in the lower digestive system. Survivors of heritable retinoblastoma who received external beam radiotherapy experienced an increased risk of subsequent primary neoplasms developing above the shoulder, whereas those who received brachytherapy were similar to those who did not receive any radiotherapy and did not experience an increased risk of subsequent primary neoplasms.

Manuscripts Arising From This Thesis Submitted to Journals for Publication

1. **Wong KF**, Reulen RC, Winter DL, Guha J, Fidler MM, Kelly J, Lancashire ER, Pritchard-Jones K, Jenkinson HC, Sugden E, Levitt G, Frobisher C and Hawkins MM. Risk of adverse health and social outcomes up to 50 years after Wilms' tumour: The British Childhood Cancer Survivor Study. *Submitted to JCO – decision of revision pending.*

Publications of the Author

1. Fidler MM, Frobisher C, Guha J, **Wong KF**, Kelly J, Winter DL, Sugden E, Whelan J, Reulen RC and Hawkins MM. Long-term adverse outcomes in survivors of childhood bone sarcoma: The British Childhood Cancer Survivor Study. *Br J Cancer 2015: 112:1857-65.*

Acknowledgements

I would like to express my thanks to those around me who have supported me through the past few years.

I would like to express special thanks to (1) my supervisors, Mike Hawkins, Raoul Reulen and Clare Frobisher for their continued support and guidance; (2) my colleagues at the British Childhood Cancer Survivor Study for their help and support: Dave Winter, Julie Kelly, Joyeeta Guha and Chloe Bright; (3) all the clinicians for their input into preparing manuscripts to journals: Kathy Pritchard-Jones, Elaine Sugden, Gill Levitt and Helen Jenkinson; (4) PanCareSurFup for the funding of my PhD; and finally (5) all the survivors who completed a 40-page questionnaire and allowed us to use their data for analyses.

I would like to thank, in particular, Raoul who acted not only as my supervisor, but also a friend for the last 3 years – all the “short chats” in your office were very encouraging.

Finally, I would like to thank my wife, Helen, for the support at home particularly during the final few weeks towards submission and my parents for all the love and support that they have given to me for the past 26 years.

Table of Contents

List of Tables

List of Figures

1 INTRODUCTION

The aim of this chapter is to provide a background to the research presented in this thesis. The chapter will discuss the improvements in survival after childhood cancer and will describe in detail potential adverse outcomes, so called “late effects” of childhood cancer and its treatment. It will then describe the study populations that form the basis of the research.

1.1 Childhood Cancer Survival

Cancer in childhood, defined here as a neoplasm diagnosed under the age of 15 years, is rare and constitutes only 0.5% of all cancers diagnosed in Great Britain[1]. Due to advances in anti-cancer therapy over several decades, survival from childhood cancer has improved substantially. In the UK, children diagnosed with cancer between 1966—1970 had overall, a 28% five-year survival rate. However, the five-year survival rate has increased substantially to 82% for those diagnosed with cancer during the period 2006–2010[2]. Similar figures have been observed in the United States (US) where, overall, 78% of children diagnosed with cancer between the years 1991–2000 survived at least five years[3]. Similarly, in Europe five-year survival for children diagnosed with cancer between the years 2000–2007, was 78% following all types of childhood cancer[4].

1.2 Types of Childhood Cancer

The substantial increase in survival rate amongst childhood cancer survivors is mainly due to improvements in anti-cancer therapy; including refinements to radiotherapy and the introduction of multi-agent combined chemotherapy. Inclusion

into clinical trials and referral to a specialist treatment centre has also had measurable impacts on survival rates[5].

Improvements in survival among those diagnosed with childhood cancer results in a growing population of childhood cancer survivors who are at an increased risk of specific adverse health and social outcomes later on in life[6-9]. These adverse health and social outcomes will be described in the next section.

For the purpose of research studies, childhood cancer is often classified into different diagnostic groups using the *International Classification of Childhood Cancers*[10]. The categories include: leukaemia, lymphoma, central nervous system (CNS) tumours, neuroblastoma, retinoblastoma, renal tumour, hepatic tumour, bone tumour, soft tissue sarcoma, germ cell tumour and other/unspecified tumours (see Appendix 8.1).

Chapter 2 and Chapter 5 of this thesis will focus on risks of adverse health and social outcomes amongst survivors of Wilms' tumour (nephroblastoma) and heritable retinoblastoma, respectively. These two childhood cancer types will be briefly described in the following sections.

1.2.1 Wilms' tumour

Wilms' tumour (WT) is a type of renal tumour that usually develops in children under five years of age, accounting for approximately 7% of all childhood tumours, and

affects approximately 80 children in the UK per year[11], however little regarding causes is known. Five-year survival has improved substantially over the last few decades from 55%, prior to the 1970s, to currently over 90%[5,12]. WT can occur in one or both kidneys (bilateral), which together with the stage of the disease, determines the treatment plan. There are five stages of Wilms' tumour[13]: (1) the tumour is residing only within the kidney; (2) the tumour has spread to nearby structures beyond the kidney but is still possible to remove with surgery; (3) the tumour has metastasised adjacent to, but beyond the kidney; (4) the tumour has metastasised to other distant parts of the body such as the lungs or liver; (5) bilateral Wilms' tumour. Most patients will receive chemotherapy before undergoing surgery to remove the whole tumour[14,15]. The surgery will try to remove the whole tumour whilst removing as little renal tissue as possible – however this is normally only performed on patients who have unilateral WT[16]. Current chemotherapy drugs often administered include Vincristine and Actinomycin-D for early stages of WT, and Doxorubicin, Cyclophosphamide, Etoposide and Carboplatin for later stages of WT[17]. Those who have bilateral WT (Stage 5) always receive chemotherapy along with surgery to both kidneys to remove as much of the tumour as possible. Radiotherapy is often given in conjunction with chemotherapy and surgery[15]. Radiotherapy doses can be varied for different stages of the tumour and depending whether it is unilateral or bilateral, but will cover a large proportion of the abdomen and also the thorax if the tumour has metastasised to the lungs[18]. Most children with WT can expect to be cured; if recurrence occurs, it is usually within 2-3 years from the original WT diagnosis[16,19].

1.2.2 Retinoblastoma

Retinoblastoma is a rare type of childhood cancer, which occurs in two forms: heritable and non-heritable. Heritable retinoblastoma (HRb) is caused by a constitutional mutation in the RB1 gene present from conception and thus lies in chromosome 13 and is inherited as an autosomal dominant with almost complete penetrance; and about 50% of offspring inherits this condition[20]. Retinoblastoma is considered as heritable if the patient has a family history of the disease or tests positive for the RB1 gene mutation[21]. Non-heritable retinoblastoma occurs through somatic mutation without any inherited predisposition. Retinoblastoma affects approximately 40 children in the UK per year and accounts for approximately 3% of all cancers in children[22]. Five-year survival of retinoblastoma has improved substantially over many decades from less than 70% in the 1970s to currently over 95%[23,24]. Most patients with RB1 will have bilateral retinoblastoma, affecting both eyes, whereas non-heritable retinoblastoma always present with just one eye affected. Historically, when retinoblastoma was diagnosed in both eyes a treatment plan was adapted to save one eye as there was a greater chance of survival compared to trying to save both eyes; one eye was enucleated and the patient would undergo radiotherapy, chemotherapy or both to eradicate the tumour in the other eye[25]. Two different types of radiotherapy treatment may be used to treat the tumour; external beam or brachytherapy (also known as internal radiotherapy where the source is implanted into the body), most commonly insertion of a radioactive plaque onto the eye. External beam delivers a defined dose of radiation to the affected area but adjacent organs may be exposed to some scattered radiotherapy, whereas radioactive plaques delivers a more focused dose to the tumour[26]. Both historically

and currently, the main chemotherapy drug used in treating retinoblastoma is the alkylating agent Cyclophosphamide. Other treatment options with potentially less adverse effects include photocoagulation and cryotherapy[27]. Photocoagulation is a laser which is used to cauterise blood vessels that supply the tumour with blood, effectively cutting off the blood supply to the tumour[28]. Cryotherapy is a treatment where the tumour cells are cooled down to an extremely low temperature to stop cell growth and eliminate abnormal tissue[29].

1.3 Risk of Adverse Health and Social Outcomes (Late Effects) after Childhood Cancer

As a result of the improvements in survival rates of childhood cancer, the number of childhood cancer survivors continues to grow and survivors still have their entire adult lifespan ahead of them[30]. Thus it is paramount that these survivors be monitored for potential long-term adverse outcomes that might occur as a result of the cancer or its treatment received. Such long-term adverse health and social outcomes – also known as “late effects” – include premature death[8,31-37], development of a second primary cancer[38-45], adverse pregnancy outcomes[46-50], educational underachievement[51-53], a decline in physical and cognitive abilities[54-56], reduced likelihood of marriage[57-60], change in smoking habits[61-63], change in alcohol consumption[63-66] and an increased risk of non-neoplastic health conditions[67-71]. Brief summaries of these late effects are described next.

1.3.1 Premature Mortality

Despite the improvement in 5-year survival rates, mortality rates for survivors of childhood cancer continue to be significantly elevated after five-year survival compared to the general population[8,31-37]. The three largest cohort studies of survivors of childhood cancer from UK[8], US[34] and Nordic countries[32] that investigated premature mortality reported an excess mortality over that seen in the general population with 10.7-fold, 8.4-fold and 10.8-fold the risk, respectively. The most common causes of death include recurrence or progression of the initial cancer, second primary neoplasms and circulatory diseases[8]. As the time after the initial cancer increases, the risk of dying from second cancers and circulatory disease increases substantially, whereas the risk of dying from recurrence or progression of the original cancer decreases[8]. By 50 years from diagnosis 30% of five-year survivors have died, where based on their demographic composition, 6% would be expected to have died[8].

1.3.2 Subsequent Primary Neoplasms

The risks of subsequent primary neoplasms (SPNs) has been investigated in different cohorts of childhood cancer survivors including the UK, US, Netherlands, Nordic countries and many other countries; and the risk was reported to be between 3 and 11-fold compared to the general population[38,72-74]. However, the risk of developing SPNs varies by initial cancer diagnosis, the treatment given and also the location of where the treatment was applied. Examples, relating to subsequent primary neoplasms in the digestive system, are provided in the following subsection.

1.3.2.1 Subsequent Primary Neoplasms in the Digestive System

Cancers in specific parts of the digestive system are briefly described, as a Chapter of this thesis will focus on the risks of developing subsequent primary neoplasms in the digestive system; in particular the oesophagus, stomach, pancreas, liver and bile duct, small intestine, gallbladder, colon, rectum and anus. The rationale for focusing on SPNs in the digestive system is due to the high number of cases of digestive cancers worldwide. Colorectal cancer is the third most prevalent cancer in the world and in combination with liver, stomach and pancreatic cancers, constitutes 24.5% of all newly diagnosed cases of cancers in 2012 worldwide and is thereby the most prevalent category of cancers[75]. Overall, survivors of childhood cancer have a 5-fold risk of developing a digestive SPN compared to the general population[38]. The background relating to the most common digestive cancers (colorectal, liver, stomach and pancreatic) will be described next.

1.3.2.2 Colorectal Cancer

In the general population colorectal cancer affects approximately 75 in 100,000 men and 57 in 100,000 women per year in the UK[76]. Colorectal cancer typically occurs during mature adulthood, past 40 years of age, where the five-year survival is 58.7%[77]. Childhood cancer survivors have a 7-fold risk of developing a colorectal cancer compared to the general population[78]. Wilms' tumour survivors are at highest risk with 16-fold risk compared to the general population[79]. Survivors who received abdominal radiation had a much higher risk (9-fold) of developing a colorectal SPN compared to those who did not receive abdominal radiation (3-fold)[79].

1.3.2.3 Liver Cancer

Primary liver cancer (which excludes metastatic liver cancer) affects 1 in 10,000 men and 1 in 20,000 women per year in the UK[80]. Liver cancer typically occurs during adulthood, past 40 years of age, where the five-year survival varies substantially dependent on the stage of the cancer. If the tumour is (1) localised (i.e. the tumour is still fully restricted within the structure of the liver), the five-year survival rate is 28%; (2) regional (i.e. the tumour has spread to nearby organs or lymph nodes), the five-year survival rate is 7%; or (3) distant (i.e. the tumour has spread to distant organs or tissue), the five-year survival rate is 2%[81]. To date, only one study has investigated the risk of liver SPN after childhood cancer and reported that childhood cancer survivors have a 25-fold risk of developing liver SPNs compared to the general population[78]. Further research is required to confirm this result and no previous study has reported the risk of liver SPN by type of First Primary Neoplasm (FPN) diagnosis – these results will be presented in Chapter 4 of this thesis.

1.3.2.4 Stomach Cancer

Stomach cancer affects 3 in 20,000 men and 2 in 25,000 women per year in the UK[82]. Stomach cancers typically occur during adulthood, past 40 years of age, where the five-year survival is 18.9%[83]. Again, only one study to date has investigated the risk of stomach SPNs after childhood cancer and reported that survivors of childhood cancer have a 13-fold risk of developing stomach SPNs compared to the general population[78]. Further research is required to confirm this result and no previous study

has reported the risk of stomach SPN by type of FPN diagnosis – these results will be presented in Chapter 4 of this thesis.

1.3.2.5 Pancreatic Cancer

Pancreatic cancer affects 7 in 50,000 men and 7 in 50,000 women per year in the UK[84]. Pancreatic cancers typically occur during adulthood, past 40 years of age, where the five-year survival is 3.3%[85]. Only one study, to date, investigated the risk of pancreatic SPN after childhood cancer and reported that survivors of childhood cancer have a 10-fold risk of developing pancreatic SPN compared to the general population[78]. Further research is required to confirm this result and no previous study has reported the risk of pancreatic SPN by type of FPN diagnosis – these results will be presented in Chapter 4 of this thesis.

1.3.3 Non-Neoplastic Health Conditions

Survivors of childhood cancer are at risk of non-neoplastic health conditions such as cardiotoxicity and nephrotoxicity[67-71] – approximately 75% of childhood cancer survivors will develop a chronic health condition at some point in their life[68,86]. Nephrotoxicity will be described in more detail, as a chapter of this thesis will focus on the risk of hospitalisation due to renal disease.

Cardiotoxicity is damage to the heart induced by radiotherapy or chemotherapy given to survivors of childhood cancer[87]. After 30 years from the initial diagnosis of cancer,

up to 16% of childhood cancer survivors will have experienced heart failure due to exposure to anthracyclines[88,89], such as doxorubicin[68,90-93]. The main conditions relating to cardiotoxicity include congestive heart failure (CHF), cardiomyopathy/heart failure, ischaemic health disease and pericardial disease. Survivors have a 6-fold risk of CHF and pericardial disease and a 5-fold risk of myocardial infarction compared to healthy siblings. The most at risk were survivors of Hodgkin's lymphoma with 7-times the risk of CHF, 12-times the risk of myocardial infarction and 10-times the risk of pericardial disease compared to healthy siblings[67] – which is likely due to the effect of radiotherapy.

Nephrotoxicity is kidney damage as a result of exposure of the kidney to toxic agents such as radiotherapy or chemotherapy given as cancer treatment. Chronic Kidney Disease (CKD) is currently affecting 6.5% of the population in England (6% male and 7% female)[94] and, in 2008, 13,895 died with chronic renal failure[95]. In comparison, a previous cohort study showed that 10.1% of childhood cancer survivors experience CKD[96,97]. There are various types of renal conditions, some of which people may be hospitalised for; which include glomerular disease (excess blood and protein in the urine), renal tubulo-interstitial disease (inflammation of the kidneys affecting interstitial area surrounding the tubules), renal failure (kidneys failing to filter waste products from the blood which is measured by the glomerular filtration rate) and urolithiasis (kidney stones). There are various potential causes of nephrotoxicity after childhood cancer including radiotherapy, chemotherapy, immunotherapy, cancer (damage to renal tissue)[98] and conditions that put a strain on the kidney such as hypertension and diabetes[99]. Chemotherapeutic drugs associated with acute

nephrotoxicity include Cisplatin and Ifosfamide and may cause chronic nephrotoxicity in up to 60% of children with cancer[100,101]. Other chemotherapeutic drugs which may cause serious damage to the kidneys are Carboplatin, Methotrexate and Nitrosoureas, although this occurrence is less common[102]. Using radiotherapy to treat children with childhood cancer may lead to radiation-induced nephritis which may further progress into renal failure[98].

1.3.4 Adverse Pregnancy Outcomes

Previous studies have shown that female survivors of childhood cancer are at risk of infertility[103-108], ovarian failure[109-114] and adverse pregnancy outcomes[46,115-117]. Survivors of specific types of childhood cancers, such as Wilms' tumour, are more prone to such adverse effects due to radiation treatment being given to the abdominal or uterine region[115,118,119]. Several previous studies found that female survivors of specific types of childhood cancers, in particular Wilms' tumour, were significantly more susceptible to adverse pregnancy outcomes including delivering offspring with low birth weight and preterm birth[46,118,120]. One American study found a significant trend between increasing radiation dose to the abdomen and increased risk of developing hypertension complicating pregnancy, early or threatened labour and malposition of foetus[47,48].

1.3.5 Health Status

Overall, health related quality of life (HRQL) for the majority of survivors of childhood cancer is reported to be very good, even when compared to the general

population[121-123]. However, this is not the case for survivors of specific types of childhood cancer: survivors of Hodgkin's disease, CNS tumours and bone tumours have been shown to have significantly reduced physical and social functioning as measured by day-to-day tasks[54,124]. A large population-based study in the UK found that survivors of bone tumours had significantly lower scores in all physical and mental components compared to the general population[54]. Others have reported that survivors experienced no difference in bodily pain, vitality and mental status after treatment for childhood cancer compared to healthy siblings[125]. Survivors of bone tumour were most at risk of reduced physical functioning in relation to day-to-day tasks whilst survivors of CNS tumours were most at risk of a reduced social functioning as measured by day-to-day tasks[54].

1.3.6 Education

Several studies have shown that survivors of childhood cancer are at risk of underachieving in terms of educational qualifications compared to the general population[51,126,127]. Survivors of childhood cancer who received cranial radiotherapy, specifically CNS tumours and leukaemia, and those who experienced neurological late effects were significantly less likely to achieve a university degree or equivalent; educational outcomes of survivors who did not receive cranial radiotherapy were found to be comparable to healthy siblings[128-130]. Two large studies from the UK[51] and the US[130] (including 10,183 and 12,430 survivors respectively) reported that survivors of Leukaemia and CNS tumours were significantly less likely to achieve a degree, or equivalent, compared to the controls. However survivors of bone tumours are more likely to achieve better educational outcomes compared to the general

population[131] – currently the majority of the research relating to educational achievement after childhood cancer is specific to CNS tumours as many survivors would have received cranial radiotherapy and therefore at risk of cognitive late effects[132]. It is equally important to analyse and disseminate results relating to educational achievement after childhood cancer for other specific subgroups of cancer[62,133-140].

1.3.7 Marriage

Approximately 30% of childhood cancer survivors get married and are approximately 20% less likely to be married compared to the general population[57,141-144]. Survivors who received radiotherapy were 31% less likely to marry compared to those who did not receive radiotherapy and males were also 20-48% less likely to be married compared to females[57,59,145]. Several studies have reported that only survivors of CNS tumour were less likely to marry compared to the general population[57,59,141,144]. However, a large UK study (including 8,155 survivors) revealed that survivors of childhood cancer were no different to the general population in terms of divorce rates. In fact survivors of non-Hodgkin's lymphoma were 45% less likely to get divorced compared to the general population[58].

1.3.8 Smoking and Alcohol

Smoking and alcohol are proven to be causes of many cancers[62,133-140]. Thus it is likely that survivors of childhood cancer, who already have an increased risk of developing a subsequent primary neoplasm, could have an even greater risk of

developing a subsequent cancer if they were smokers or consume excessive amounts of alcohol. Survivors of childhood cancer were 49% less likely to smoke with 19.8% of the survivors reported to regularly smoke and 60% less likely to consume harmful amounts of alcohol with 3.9% of the survivors reported to consume harmful amounts of alcohol[61,64]. Survivors of all types of childhood cancer, except non-heritable retinoblastoma, were significantly less likely than the general population to smoke and survivors of all types of childhood cancer, except for non-irradiated leukaemia, soft tissue sarcoma and bone tumours, were significantly less likely to consume harmful amounts of alcohol[61,64].

The research to be presented in this thesis should help clinicians risk stratify survivors in long-term follow-up clinics and provide evidence for updating clinical follow-up guidelines for survivors of childhood cancer. In this thesis, four original studies will be presented, with each study contributing new results which have previously not been investigated; adverse outcomes will be investigated in survivors of Wilms' tumour with up to 50 years of follow up; adverse outcomes will be investigated in survivors of heritable retinoblastoma by specific types of radiotherapy using a population-based cohort; risks of hospitalisation due to specific renal diseases in childhood cancer survivors will be investigated; and risks of SPNs in specific sites of the digestive system will be investigated.

1.4 Data

Data relating to two cohorts were used for the analysis of this thesis; The British Childhood Cancer Survivor Study (BCCSS) and the PanCareSurFup (PCSF) study. The BCCSS cohort was used for investigations into (i) the risk of long-term adverse health and social outcomes among Wilms' tumour survivors, (ii) the risk of long-term adverse health and social outcomes in survivors of heritable retinoblastoma, and (iii) the risk of hospitalisation due to a renal disease after childhood cancer. The PCSF cohort was used to investigate the risks of developing a second primary cancer of a digestive organ in a European setting. A detailed description of both cohorts presented below.

1.4.1 The British Childhood Cancer Survivor Study

The British Childhood Cancer Survivor Study is a population-based cohort study of 17,980 five-year survivors of childhood cancer diagnosed with cancer between 1940 and 1991 under the age of 15 in the UK. The study was recently extended to include survivors diagnosed with childhood cancer up to 2006, bringing the total to 34,489 five-year survivors of childhood cancer. The BCCSS study was established to investigate the risks of adverse health and social outcomes after surviving cancer for five years.

Survivors of childhood cancer were eligible to be included in the BCCSS cohort if they were diagnosed during the period 1940 to 2006, less than 15 years of age and subsequently survived for at least five years. The cohort was ascertained using the

population based National Registry of Childhood Tumours (NRCT). Since the 1970's, over 97% of all childhood cancer registrations were picked up by the NRCT[146]. All of these childhood cancer registrations were extracted for the BCCSS and because we had received approval from the multicentre research ethics committee and all the local research ethics committees, we did not require individual patient consent. However, survivors had the choice of opting out of the study which was fewer than 10 in total.

All survivors who were eligible within the original cohort, diagnosed between 1940–1991, were sent a package via their primary care physician (PCP), or GP. To be eligible they needed to be alive and at least 16 years of age. The package sent to the GP contained four items; (i) a cover letter that explained the objectives of the BCCSS, (ii) a consent form for the survivor should they decide to participate in the study along with a pre-paid return envelope, (iii) a drafted invitation letter for the PCP to send to the survivor along with the BCCSS questionnaire and (iv) a pre-paid package to be mailed to the survivor with the items from iii. The package sent, by the GP, to survivors contained; (i) the suggested covering letter from the GP inviting survivors to participate in the BCCSS, (ii) a covering letter from the study co-ordinating centre; (iii) a leaflet with brief explanation of the study; (iv) a copy of the male or female study questionnaire (this would depend on whether the survivor was male or female) and (v) a pre-paid envelope for the survivor to return the completed questionnaire to the study co-ordinating centre.

It was predicted that some survivors, as a result of their childhood cancer, would not be able to complete the questionnaire by themselves – in these circumstances, a third party (usually a relative) would complete the form with as much information from the survivor as possible. A free telephone helpline was established for both survivors and PCP if they had difficulties, problems or wished to ask questions pertaining to the BCCSS study or the questionnaire. Treatment information relating to the survivors' initial cancer diagnosis was extracted from previous medical records by the Childhood Cancer Registry Group (CCRG) in a 'yes', 'no' or 'no record' format for each of the possible treatments; surgery, radiotherapy and chemotherapy.

The Multi-Centre Research Ethics Committee (MREC) and each of the 212 Local Research Ethics Committees (LREC) in Britain gave approval for the British Childhood Cancer Survivor Study.

Specific results arising from the questionnaire will be presented in Chapter 2 and Chapter 5, which utilises the cohort from the BCCSS, such as pregnancy outcomes, educational achievements, smoking status, alcohol consumption, marital status, health-status (SF-36) and the use of health services.

1.4.2 PanCareSurFup Cohort

The *PanCare Childhood and Adolescent Cancer Survivor Care and Follow-up Studies* cohort, abbreviated to PanCareSurFup, comprises of more than 115,000 survivors of childhood cancer who were diagnosed under the age of 20 from 1940 to

2008 and identified in both national and hospital-based registries in France, Hungary, Italy, Netherlands, Denmark, Sweden, Norway, Finland, Iceland, Slovenia, Switzerland and UK[147]. The PCSF cohort comprises 3,138 five-year survivors from France diagnosed between the period 1946 and 1986; 4,885 five-year survivors from Hungary diagnosed between the period 1971 and 2008; 10,781 five-year survivors from the population-based registries in Italy diagnosed between the period 1964 and 2005; 9,192 five-year survivors from the hospital-based registries in Italy diagnosed between the period 1960 and 2008; 6,044 five-year survivors from Netherlands diagnosed between the period 1963 and 2001; 4,832 five-year survivors from Denmark diagnosed between the period 1943 and 1998; 7,709 five-year survivors from Sweden diagnosed between the period 1958 and 1998; 3,877 five-year survivors from Norway diagnosed between the period 1953 and 1997; 6,229 five-year survivors from Finland diagnosed between the period 1953 and 2006; 274 five-year survivors from Iceland diagnosed between the period 1955 and 1998; 1,252 five-year survivors from Slovenia diagnosed between the period 1960 and 2002; 4,373 five-year survivors from Switzerland diagnosed between the period 1964 and 2005; 17,960 five-year survivors from UK diagnosed between the period 1940 and 1991.

One of the main objectives of the PCSF case-control study is to ascertain the risks of three outcomes following survival from childhood cancer; (1) cardiac conditions, (2) subsequent primary cancers and (3) late mortality. This will be achieved by analysing the European-wide data and to publish and disseminate the results.

Although this thesis only presents results from the PCSF cohort study, three case-control studies are currently being established that includes childhood cancer

survivors relating to late mortality, subsequent primary cancers and cardiac events which have been systematically ascertained and validated. The PCSF case-control study, relating to subsequent primary cancers, will specifically focus on carcinomas that are common to the general population after 40 years of age; specifically digestive and genitourinary sites. Radiation dosimetry will be undertaken for survivors included within these case-control studies to obtain estimates of radiation doses corresponding to the sites of the FPN and compared to controls. The absolute risk of each of the three outcomes (specified above) will be estimated and comparisons will be made to general population rates, especially for those aged 40 years or more.

1.5 Rationale and Aim

Treatment for cancer can lead to many adverse health and social outcomes later on in life. Important outcomes to consider are premature death, second cancers, health status, marriage, pregnancy, educational achievement, smoking and alcohol consumption which all have an impact on the quality of life after cancer[8,31-66]. Generally, childhood cancer survivors have a longer life ahead of them compared to survivors of adult cancers and therefore have a longer period to experience adverse effects from the treatment given for the initial cancer. The evidence of risks of adverse health and social outcomes presented should help in the risk stratification of survivors for appropriate level of intensity of clinical follow-up, help updating clinical follow-up guidelines and provide evidence relevant to the evaluation of components of future treatment protocols from a risk, as well as a benefit, perspective.

A large number of previous studies on the late effects following childhood cancer were not population-based or have been based on relatively small numbers of childhood cancer survivors or limited follow-up of survivors. This thesis aims to contribute to the knowledge of adverse outcomes following survival after childhood cancer by addressing some of these limitations. In order to achieve this we will focus on four key areas by using the BCCSS and PCSF cohorts, which will allow us to provide reliable evidence—using large numbers of childhood cancer survivors from population-based cohorts—to health care providers and survivors of childhood cancer as well as government funded bodies to re-evaluate risks of late effects so that current follow-up and surveillance plans may be improved.

In particular, the four aspects of focus is to investigate:

(1) The risks of adverse health and social outcomes in survivors of Wilms' tumour up to 50 years from diagnosis in the BCCSS cohort;

(2) The risk of hospitalisations due to specific renal diseases following survival from childhood cancer in the BCCSS cohort;

(3) The risks of developing second cancers in the digestive system after childhood cancer in the PCSF cohort;

(4) The risks of adverse health and social outcomes in survivors of heritable retinoblastoma beyond 50 years from diagnosis in the BCCSS cohort.

These key areas were dictated by my particular interest in renal tumours and the following late effects such as renal diseases and secondary malignancies in the abdominal region. Originally, the fourth topic was intended to be a case-control study investigating the risks of second digestive cancers with full radiotherapy and chemotherapy dosimetry in the PanCareSurFup study, which would have followed from the third topic. However, due to unforeseen circumstances, the data was not available in time for analysis and we decided to conduct research into another group of cancer survivors using the BCCSS data.

1.6 Thesis Framework

Chapter 2 of the thesis will explore survivorship following Wilms' Tumour investigating various adverse health and social outcomes. This will include late mortality, subsequent cancers, adverse pregnancy outcomes, health status using the SF-36 questionnaire, use of health care services and social outcomes. In Chapter 3, the risks of being hospitalised due to specific renal diseases are investigated. We explore the different types of renal morbidities, such as glomerular disease, renal tubulo-interstitial (RTI) disease, renal failure, urolithiasis and other types of kidney and urinary diseases, which patients are admitted to hospital for and compare these admissions to those from the general population to assess the risk. Chapter 4

investigates the risk of developing subsequent cancers in the digestive system using the largest European cohort assembled to date. This is the first study to investigate the risks of cancers in specific sites of the digestive system by FPN type. Chapter 5 explores the adverse health and social outcomes (similar to that in Chapter 2) but following heritable retinoblastoma and investigating primarily the risk of developing subsequent cancers in survivors who received different applications of radiotherapy. In Chapter 6 the main findings, potential implications for guidelines, study limitations and recommendations for future research are discussed.

2 RISK OF ADVERSE HEALTH AND SOCIAL OUTCOMES UP TO 50 YEARS AFTER WILMS' TUMOUR: THE BRITISH CHILDHOOD CANCER SURVIVOR STUDY.

Abstract

Purpose: Wilms' tumour (WT) survivors are at risk of adverse health and social outcomes but risks beyond 30 years from diagnosis remain uncertain. We investigated risks of adverse outcomes among 5-year survivors of WT, particularly between 30 and 50 years from diagnosis.

Patients and Methods: British Childhood Cancer Survivor Study includes 1,441 5-year survivors of WT. We investigated cause-specific mortality, risk of subsequent primary neoplasms (SPNs)—and for those who completed a questionnaire—extent of smoking and drinking, educational achievement, health-status and health service use compared to the general population.

Results: Cumulative risk of death, from all causes excluding recurrence, increased substantially from 5.4% by 30 years after WT diagnosis to 22.7% by 50 years—75% of excess deaths beyond 30 years from diagnosis were attributable to SPNs (50%) and cardiac diseases (25%). Digestive cancer (most frequently bowel) accounted for 41% of the excess cancers beyond 30 years.

Conclusion: Between 30 and 50 years from diagnosis, survivors of WT are at a substantially increased risk of premature mortality and 75% of the excess deaths were accounted for by SPNs and cardiac diseases. Radiotherapy exposure was a risk factor for both outcomes. The proportion of WT patients exposed to radiotherapy has reduced substantially in recent decades from initiatives like the SIOP WT 2001 clinical trial which sought to reduce late effects. However the majority of current survivors, at least 30 years from diagnosis, received radiotherapy. Surveillance of this group should focus on SPNs (particularly bowel and breast cancers) and cardiac conditions.

2.1 Introduction

Advances in anti-cancer therapy have led to five-year survival after WT improving to 90%[5]. Although WT is increasingly curable, survivors are at risk of a range of treatment related long-term adverse health and social outcomes. WT survivors have increased mortality compared to the general population[8,148], are at excess risk of developing second primary cancers[38,148-150], adverse pregnancy outcomes[46-48], cardiac disease and renal dysfunction[151].

Although a number of previous studies investigated the risks of adverse health and social outcomes among WT survivors[12,48,50,103,109,152,153], none had sufficient follow-up to investigate the risks beyond 30 years from WT diagnosis satisfactorily, hence there remains considerable uncertainty regarding the magnitude of these risks. The main advantage of the current study—in addition to being large-scale and population-based—is that 65% of the cohort survived for more than 30 years from WT diagnosis.

The objective of this study was to investigate risks of adverse health and social outcomes among 5-year survivors of WT up to 50 years from diagnosis. Specific objectives were to investigate: (i) cause-specific late mortality; (ii) risks of developing subsequent primary neoplasms (SPNs); (iii) risks of adverse pregnancy outcomes; (iv) health-status; (v) smoking and alcohol consumption, educational attainment and marriage status; (vi) health services use.

2.2 Methods

British Childhood Cancer Survivor Study (BCCSS)

The British Childhood Cancer Survivor Study (BCCSS) is a large-scale population-based cohort study established to investigate adverse health and social outcomes among such survivors. The BCCSS includes 1,441 survivors of WT—who were diagnosed before 15 years of age, between 1940 and 1991 in Great Britain, and who survived for at least five years[154]. The BCCSS cohort was ascertained through the population-based National Registry of Childhood Tumours. Limited treatment information was obtained from clinical records to the level of detail given in Table 2.5.1.

Ascertainment of deaths and subsequent primary neoplasms

Ascertainment of deaths (including underlying cause of death) and SPNs in the BCCSS was achieved through flagging of the entire cohort of childhood cancer survivors at the NRCT. Flagging informs the BCCSS when a survivor dies or develops a SPN by providing linkage between the population-based cohort and the national population-based death and cancer registration systems. Confirmation of all SPNs was undertaken by writing to relevant clinician(s) to obtain all diagnostic, particularly pathology reports[38]. Validation of causes of deaths was undertaken by two clinicians (Elaine Sugden and Gill Levitt) by reviewing all available clinical records, in addition to the death certificates, to ascertain the underlying cause of death. Consequently, all SPNs and causes of death were validated.

BCCSS Questionnaire

Between 2001 and 2007, all survivors who were alive and aged over 16 years were sent a 40-page questionnaire by their primary care physician on behalf of the BCCSS. In total, 947 (70.5%) of all eligible Wilms' survivors completed and returned the questionnaire[154]. The BCCSS questionnaire inquired about potential adverse health and social outcomes of childhood cancer and its treatment including questions regarding health-status (SF-36), health services use, medical conditions, medical procedures, marriage, adverse pregnancy outcomes (e.g. miscarriage, stillbirth, preterm birth), smoking and alcohol consumption and educational achievements.

Ethical approval for the BCCSS was obtained from the relevant Multi-Centre Research Ethics Committee and every Local Research Ethics Committee in Britain (212 in total).

Statistical Analysis

Cause-Specific Mortality

Numbers of observed deaths among WT survivors were compared with the number of expected deaths based on the population of England & Wales. The period at risk began 5 years following initial diagnosis of childhood WT until the first occurrence of emigration, death or exit (31st December 2010). Standardised mortality ratios (SMR) for specific causes of death were calculated as the ratio of observed over expected number of deaths. Absolute excess risks (AERs) were calculated from the observed minus expected number of deaths divided by the number of person-years at risk

multiplied by 10,000. Cumulative mortality for specific causes of death was estimated by treating other causes of death as competing risks[155].

Subsequent Primary Neoplasms

The period at risk of developing a SPN began 5 years from diagnosis of WT and continued until the first occurrence of SPN, emigration, death or exit (31st December 2006). Multiple observed SPNs per survivor were permitted for comparisons with those expected from the general population to avoid bias, but only the first SPN was considered in measures of cumulative risk. Standardised incidence ratios (SIRs), AERs and cumulative risk of developing an SPN were calculated as described above in relation to death.

Health-status – *"Short Form 36"*

Health-status was measured using the SF-36 questionnaire[54]. To compare SF-36 scale scores observed among WT survivors with the general population, normative data from the Oxford Healthy Life Survey (OHLS) were used[156]. The OHLS is a general population survey conducted between 1991 and 1992 that included 13,042 individuals aged 18-64 years randomly sampled from the Family Health Service Authority registers in Oxfordshire, Berkshire, Buckinghamshire and Northamptonshire. For each SF-36 scale, the difference in mean scores between survivors of WT and OHLS was calculated using linear regression which adjusted for age and sex. Also, we examined responses to the individual questions (items) underlying the specific SF-36 scales by comparing the directly standardised

percentage (for age and sex) of WT survivors that reported a limitation or other problem to that reported by the general population.

Adverse Pregnancy Outcomes

To investigate the risks of adverse pregnancy outcomes, logistic regression models were used to calculate odds ratios (ORs) to compare likelihood of low birth weight, preterm births and miscarriage between pregnancy outcomes among female survivors of WT who were treated with abdominal radiotherapy with female survivors of non-WT childhood cancers who did not receive abdominal radiotherapy (comparison with UK population pregnancy rates was not possible as there is currently no database which holds information relating to the rates of adverse pregnancy outcomes). Most female WT survivors, who reported being pregnant at least once, had been treated with abdominal irradiation (87%).

Smoking status, alcohol consumption and education level

Among those WT survivors who completed the BCCSS questionnaire, smoking and alcohol consumption and educational attainment were compared to the general population by using data from the nationwide General Household Survey (GHS)[157]. Adjustment for confounders and classification of current regular smokers, alcohol consumption and educational attainment has been defined in previous BCCSS studies[51,61,64]. For each outcome, ORs comparing WT survivors to the GHS were calculated using multivariable logistic regression with a generalized estimating equation modification that took into account clustering within the GHS; these ORs were adjusted for attained age and sex.

Marital status

To investigate marital status among WT survivors, ORs of ever being married—stratified by sex and attained age—were calculated using data from the National Marriage Registry as the reference population[57]. Age-specific ORs were then pooled into one overall OR by using the Mantel-Haenszel method for combining ORs[158].

Health services use

Frequency of consultations with a doctor, hospital outpatient visits, day-patient hospitalisations and inpatient hospitalisations were evaluated by calculating ORs—comparing WT survivors with the GHS— using a multivariable logistic regression model. ORs were adjusted for attained age, sex, educational attainment and stratified by whether survivors were on regular long-term hospital follow-up in relation to their childhood cancer and its treatment[159].

Statistical significance for all analyses was defined as a 2-sided $P<0.05$. All analyses were carried out in Stata 12 (StataCorp, College Station, Texas).

2.3 Results

Cohort Characteristics

From the total of 1,441 WT survivors in the cohort, 10% (N=146) had died, 2% (N=31) emigrated and 88% (N=1264) were alive at the exit date (31st December 2010). Characteristics of WT survivors who completed the questionnaire were similar to all WT survivors in the BCCSS cohort (Table 2.5.1). In relation to mortality there were 38,803 person-years subsequent to 5-year survival with mean and median

follow-up of 26.9 and 26.0 years, respectively. Table 2.5.1 indicates that 82% (756/920) of the survivors were exposed to direct abdominal radiotherapy and only 164 were known to be unexposed. Consequently analysis of the entire cohort, used for analysis of deaths and SPNs, corresponds to a group overwhelmingly exposed to direct abdominal radiotherapy.

Causes-Specific Mortality

Survivors experienced over 5 times the number of deaths expected (SMR=5.4; 95%CI: 4.6,6.4) with 30.7 additional deaths (95%CI: 24.6,36.8) per 10,000 person-years in excess of that expected (Table 2.5.2). For specific causes of death with at least 20 observed deaths results are reported separately. In multiplicative terms, cause-specific mortality was highest for SPNs (SMR=7.3; 95%CI: 5.3,9.8) and cardiac disease (SMR=10.1; 95%CI: 6.5,14.9). In terms of the AER, the highest excess which accounted for 32% of all excess deaths related to SPNs, followed by deaths due to recurrence and cardiac causes which accounted for 21% and 19% of the excess deaths, respectively. Deaths due to recurrence mostly occurred relatively early with 22/25 such deaths between 5-14 years, 3/25 between 15-24 years and none from 25 years from diagnosis (not shown in tables). The AER due to all causes of death except recurrence was 14 excess deaths (per 10,000 person-years) between 5-29 years after WT diagnosis, but increased 8-fold to 108.4 excess deaths beyond 30 years – which is equivalent to 1 extra death per 100 survivors each year (Table 2.5.3). From 30 years subsequent to WT diagnosis deaths from SPNs and cardiac disease accounted for 50% and 25% of the total number of excess deaths, respectively.

Cumulative mortality due to recurrence was 1.8% by 30 years after WT diagnosis, and remained the same by 50 years as there were no more deaths due to recurrence. Cumulative mortality due to all causes except recurrence was 5.4% by 30 years after WT diagnosis, but increased substantially to 22.7% by 50 years. By 50 years from WT diagnosis, the cumulative mortality from SPNs and cardiac diseases were 8.2% and 6.3%, respectively (Figure 2.5.1).

There were 25 cardiac deaths according to the underlying cause of death on the death certificate and we summarise the results of a comprehensive review of these causes of death taking account of all hospital records and autopsy reports still available (Table 2.5.7). This comprehensive review ascertained that 4 deaths were due to renal failure; 9 myocardial infarction (4 with chest irradiation and/or lung metastases); 7 cardiomyopathy/heart failure (6 with chest irradiation); 3 pulmonary embolism; 2 other causes.

Subsequent Primary Neoplasms

The cumulative risk of developing an SPN was 3.7% (95%CI: 2.7,5.0) by 30 years after WT diagnosis increasing to 16.4% (95%CI: 10.7,23.2) by 50 years (Figure 2.5.2). The most common SPN were those of digestive sites, which occurred in 17 WT survivors, 7 were bowel cancers and the other affected sites are specified in Table 2.5.4; all 17 had previously received abdominal radiotherapy. Over 40% of SPNs developed beyond 30 years from diagnosis of WT, for digestive SPNs 10 of 17 developed in this period and these accounted for 41% of the excess number of

cancers in this period of follow-up. All WT survivors who developed breast cancer had previously received either abdominal or chest radiotherapy.

Health-status (SF-36)

WT survivors scored significantly lower than the general population on two of the eight SF-36 scales: physical functioning (difference in means, D=-1.8; 95%CI: -3.3,-0.9) and general health perception (D=-6.7; 95%CI: -8.1,-5.2) (Table 2.5.5). However, WT survivors reported significantly better role-emotional functioning (D=3.4; 95%CI: 1.2,5.6) than the general population. When examining the responses to individual questions which comprise the physical functioning scale, WT survivors reported significantly higher limitations on most items compared to the general population (Figure 2.5.3). When examining responses to the individual questions which comprise the general health perception scale, WT survivors reported higher agreement that their health was worse in relation to each question compared to the general population (Figure 2.5.4).

Pregnancy Outcomes

Of the 511 female WT survivors who completed the BCCSS questionnaire, 412 pregnancies were reported by 184 females of which 32% resulted in low birth weight, 35% in a preterm delivery and 22% in a miscarriage for those who responded to the relevant questions and had received abdominal irradiation. Female survivors of WT treated with abdominal radiotherapy were at higher risk of giving birth to a low birth weight baby (OR=3.3; 95%CI: 2.2,4.9) and giving birth preterm (OR=3.1; 95%CI: 2.1,4.7) compared to non-WT survivors of childhood cancer not treated with

abdominal radiotherapy. Pregnancy analyses were stratified by eras of treatment (<1970 and ≥1970), however no statistical differences were found (p≥0.386).

Smoking, Alcohol, Education and Marriage

Compared to the general population, WT survivors were less likely to be a regular smoker (OR=0.7; 95%CI: 0.6,0.8), consume alcohol (OR=0.7; 95%CI: 0.6,0.9) or consume harmful amounts of alcohol (OR=0.5; 95%CI: 0.3,0.7). WT survivors did not significantly differ from the general population in achieving specific levels of education (all p-values>0.05). Male survivors were significantly less likely to be married (OR=0.7; 95%CI: 0.5,0.9) compared to the general population.

Health services use

Compared to the general population, survivors of WT were significantly more likely to attend hospital outpatients (OR=2.6; 95%CI: 2.2,3.1) at least once in the last 3 months, be hospitalised as a day patient (OR=1.7; 95%CI: 1.3,2.1) at least once in the last year and be hospitalised as an inpatient (OR=2.0; 95%CI: 1.6,2.6) at least once in the last year. When stratified by whether WT survivors were on long-term hospital follow-up in relation to their childhood cancer or its treatment, survivors not on long-term hospital follow-up (N=546) were still significantly more likely to be hospitalised as an outpatient (OR=2.1; 95%CI: 1.7,2.6), day patient (OR=1.5; 95%CI: 1.1,2.0) and inpatient (OR=1.9; 95%CI: 1.4,2.6) compared to the general population; whilst survivors on such long-term hospital follow-up (N=360) were even more likely

to be hospitalised as an outpatient (OR=3.5; 95%CI: 2.7,4.6), day patient (OR=1.9; 95%CI: 1.3,2.7) and inpatient (OR=2.3; 95%CI: 1.6,3.5).

2.4 Discussion

New findings include the identification of a substantial increase in cumulative mortality due to causes of death other than recurrence in the period from 30 to 50 years after WT diagnosis increasing from 5.4% to 22.7%, corresponding to 1 extra death per 100 survivors per year. Consistent with our study, a previous US based large-scale study[148] found that cumulative mortality at 30 years from WT diagnosis was approximately 3%, but thus far—to our knowledge—no study has demonstrated the substantial increase in mortality from 30 to 50 years from WT diagnosis. The excess of deaths after 30 years was mainly attributable to SPNs (50%) and cardiac (25%) related deaths which together accounted for 75% of all excess deaths. The absolute excess risk for the first 30 years following diagnosis is consistent with that found in the National Wilms' Tumor Study[160]; but this study also did not have sufficient follow-up to demonstrate a substantial increase in the absolute excess risk beyond 30 years from diagnosis as observed in the present study.

The excess of SPNs during the initial 30 years from WT was comparable to that reported in previous studies[44,145]. Beyond 30 years from WT, previous studies had insufficient follow-up to satisfactorily assess evidence for an excess. Our cumulative risk increased from 3.7% by 30 years to 16.4% by 50 years. Beyond 30 years from WT there were 4.5 excess cancers observed per 1,000 per year, this excess was mainly attributable to digestive cancers (41%) and breast cancers (7%) – together

accounting for 48% of the total excess of cancers. All WT survivors who developed a digestive SPN had received abdominal radiotherapy and all survivors who developed breast cancer received either abdominal or chest radiotherapy. We have previously reported the strong link between abdominopelvic irradiation and subsequent bowel cancer[161], specifically the risk of developing bowel cancer among childhood cancer survivors treated with direct abdominopelvic irradiation is at least that observed among individuals who have at least 2 first-degree relatives diagnosed with bowel cancer, and for whom colonoscopy is currently recommended from ages 35 to 45[162] or from age 50[163]. This raises the serious question of whether irradiated Wilms' survivors, which comprise the majority of childhood cancer survivors treated with direct abdominopelvic irradiation, should be similarly recommended for colonoscopy.

Previous studies have shown that survivors of WT reported adverse health-status outcomes comparable to our study[148,164], that is, lower general health perception and physical function. In addition, WT survivors also reported lower overall health-status in previous studies[153,165-167]. WT survivors in our study reported that role-emotional was significantly higher than OHLS, however, this is likely due to ceiling effects as role-emotional were measured by 3 categories causing a clustering of scores at the maximum level[168].

Consistent with previous studies[46-48,50,169], completed pregnancies were more likely to be premature and result in low birth weight. The results of the current and previous studies suggest that female survivors treated with abdominal radiation should be carefully monitored during pregnancy.

With respect to social outcomes, and consistent with previous studies, WT survivors appear to have a healthier life style being less likely a regular smoker[63,170] and consuming lower amounts of alcohol than the general population. Similar to a previous study, male survivors were less likely to be married than the general population[171].

WT survivors were more likely to visit the hospital and also were more likely to be hospitalised irrespective of whether they were on regular long-term hospital follow-up in relation to their childhood cancer or its treatment, a finding that is similar to previous studies[148,172].

Study Limitations

A limitation of our study was the lack of detailed information on radiotherapy and chemotherapy exposures given for WT – detailed review of the results may allow inferences to be suggested and hypotheses to be generated that could be tested in future studies. It is also important to acknowledge that survivors included in the cohort were treated between 1940 and 1991 and hence our findings are unlikely to be generalisable to survivors treated in more recent years due to changes in exposure to different treatments. For example, the vast majority (82%) of the survivors presented here had received radiotherapy as part of initial treatment. In contrast, only 27% of non-anaplastic Wilms' tumour patients included within a relatively recent randomised clinical trial (UKW3)[173], which recruited between 1991 and 2001, received radiotherapy as part of initial treatment. Nevertheless there is still an entire cohort of survivors being seen in follow-up clinics, or discharged into the community, who were treated before 1991 and our evidence relates directly to them.

Conclusion

Between 30 and 50 years from diagnosis, survivors of WT are at a substantially increased risk of premature mortality and 75% of the excess deaths were accounted for by SPNs and cardiac diseases. Radiotherapy exposure was a risk factor for both outcomes. The proportion of WT patients exposed to radiotherapy has reduced substantially in recent decades, from initiatives like the SIOP WT 2001 clinical trial which sought to reduce late effects[173]. However the majority of current survivors, at least 30 years from diagnosis, received radiotherapy. Surveillance of this group should focus on SPNs (particularly bowel and breast cancers) and cardiac conditions as these account for 50% and 25% of the total excess deaths observed, respectively.

2.5 Tables and Figures

Table 2.5.1 Characteristics of all 1,441 Wilms' tumour (WT) survivors in the British Childhood Cancer Survivor Study and of all those who completed a questionnaire.

		All WT Survivors (N = 1,441)	Completed Questionnaire Returned (N = 947)	No Completed Questionnaire Returned (N = 494)
Sex	Male	733 (51%)	436 (46%)	297 (60%)
	Female	708 (49%)	511 (54%)	197 (40%)
Age at Diagnosis (years)	Mean	3.3	3.3	3.3
	Median	2.8	2.9	2.7
	0 – 4	1156 (80.2%)	760 (80.3%)	396 (80.2%)
	5 – 9	252 (17.5%)	166 (17.5%)	86 (17.4%)
	10 – 14	33 (2.3%)	21 (2.2%)	12 (2.4%)
Age at Questionnaire Completion[1] (years)	Mean	n/a	28.3	n/a
	5 – 9	n/a	0 (0.0%)	n/a
	10 – 19	n/a	221 (23.3%)	n/a
	20 – 29	n/a	350 (37.0%)	n/a
	30 – 39	n/a	261 (27.6%)	n/a
	40 – 49	n/a	90 (9.5%)	n/a
	50 – 59	n/a	22 (2.3%)	n/a
	60+	n/a	3 (0.3%)	n/a
Years from WT diagnosis[2] (years)	5-9	30 (2.1%)	0 (0.0%)	30 (6.1%)
	10-19	94 (6.5%)	27 (2.9%)	67 (13.6%)
	20-29	349 (24.2%)	234 (24.7%)	115 (23.3%)
	30-39	652 (45.2%)	455 (48.0%)	197 (39.9%)
	40+	316 (21.9%)	231 (24.4%)	85 (17.2%)
On long-term hospital follow up[3]	Yes	n/a	360 (38.3%)	n/a
	No	n/a	546 (58.0%)	n/a
	Missing	n/a	35 (3.7%)	n/a
Treated with abdominal radiotherapy	Yes	756 (52.5%)	489 (51.7%)	267 (54.1%)
	No	164 (11.4%)	111 (11.7%)	53 (10.7%)
	Missing	521 (36.1%)	347 (36.6%)	174 (35.2%)
Treated with chemotherapy	Yes	701 (48.6%)	460 (48.6%)	241 (48.8%)
	No	203 (14.1%)	125 (13.2%)	78 (15.8%)
	Missing	537 (37.3%)	362 (38.2%)	175 (35.4%)
Surgery	Yes	921 (63.9%)	598 (63.2%)	323 (65.4%)
	No	13 (0.9%)	9 (0.9%)	4 (0.8%)
	Missing	507 (35.2%)	340 (35.9%)	167 (33.8%)

[1] The BCCSS questionnaire was sent out to survivors aged 16 or over.

[2] Years of follow-up after initial diagnosis; percentages correspond to the total number in cohort or completed questionnaire.

[3] Regular hospital follow-up appointments in relation to the childhood cancer or its treatment.

Table 2.5.2. Cause-specific standardised mortality ratios (SMRs) and absolute excess risks (AERs) for 1,441 survivors of Wilms tumour.

Cause of death	Obs/Exp	SMR (95%CI)	AER (95%CI)[ǂ]	% of Total AER
All Causes Overall	146 / 26.8	5.4 (4.6 , 6.4)	30.7 (24.6, 36.8)	100%
Years from diagnosis				
5 – 9 Years				
10 – 19 Years	25 / 1.6	15.7 (10.2, 23.2)	36.2 (21.0, 51.3)	
20 – 29 Years	29 / 6.1	4.8 (3.2, 6.9)	16.5 (8.9, 24.0)	
30 – 39 Years	37 / 6.8	5.5 (3.8, 7.5)	21.1 (11.1, 31.1)	
40+ Years	27 / 5.9	4.6 (3.0, 6.6)	38.2 (19.8, 56.7)	
	28 / 6.5	4.3 (2.9, 6.3)	92.7 (48.1, 137.4)	
Infection	5 / 0.6	8.7 (2.8 , 20.2)	1.1 (0.0, 2.3)	4%
Recurrence	25 / 0	-	6.4 (3.9, 9.0)	21%
SPN	44 / 6.0	7.3 (5.3 , 9.8)	9.8 (6.4 , 13.1)	32%
Blood	0 / 0.1	NA	0.0 (NA)	0%
Endocrine	0 / 0.6	NA	-0.1 (-0.1, -0.1)	0%
Mental	1 / 0.9	1.1 (0.0 , 6.2)	0.0 (-0.5, 0.5)	0%
Nervous	3 / 1.3	2.2 (0.5 , 6.6)	0.4 (-0.4, 1.3)	1%
Cardiac	25 / 2.5	10.1 (6.5 , 14.9)	5.8 (3.3, 8.3)	19%
Respiratory	6 / 1.2	4.9 (1.8 , 10.7)	1.2 (0.0, 2.5)	4%
Digestive	6 / 1.5	3.9 (1.4 , 8.5)	1.2 (-0.1, 2.4)	4%
Muscoskeletal	0 / 0.2	NA	0.0 (NA)	0%
Genitourinary	6 / 0.2	33.1 (12.2 , 72.1)	1.5 (0.3 , 2.7)	5%
Perinatal	2 / 0.7	3.0 (0.4 , 10.8)	0.3 (-0.4 , 1.1)	1%
External	19 / 9.6	2.0 (1.2 , 3.1)	2.1 (0.2 , 4.6)	7%
Other	4 / 1.4	2.9 (0.8 , 7.3)	0.7 (-0.3 , 1.8)	2%

Calculation of SMR for deaths due to recurrence of Wilms' tumour would not be appropriate since the expected mortality rate in the general population would be 0. AER for recurrence was calculated as the incidence rate per 10,000 person-years. Confidence intervals for SMR were calculated using the approximate method where the number of deaths≥100 and the Poisson exact method where number of deaths<100 [174]. Perinatal deaths refer to causes resulting from congenital abnormalities (2). External causes of death comprise accidents (7 motor accidents and 5 accidental poisoning), suicides (2) and other (one death could not be determined as accident or suicide and one death was due to a medical procedure). Other causes of death were either unknown or ill-defined (2) or due to general symptoms (1)and stroke (1). ǂ Overall AER for all causes of death was 30.7 per 10,000 person-years, but due to rounding, the specific causes of death sum to 30.4.

Table 2.5.3. AER of specific causes of death by years of follow-up as a proportion of total absolute excess risk.

Cause of Death	AER < 30 Years from diagnosis			AER ≥ 30 Years from diagnosis		
	Obs/Exp	AER (95%CI)	% of Total AER	Obs/Exp	AER (95%CI)	% of Total AER
Recurrence	25 / 0	7.2 (4.4-10.0)	34%	0 / 0	0.0 (NA)	0%
SPN	18 / 2.8	4.4 (2.0-6.8)	21%	26 / 3.2	53.8 (30.2-77.4)	50%
Cardiac	12 / 0.9	3.2 (1.2-5.2)	15%	13 / 1.5	27.0 (10.3-43.7)	25%
External	14 / 8.3	1.6 (-0.5-3.7)	7%	5 / 1.2	8.9 (-1.4-19.2)	8%
All Other Causes	22 / 5.5	5.0 (2.3-7.7)	23%	11 / 2.9	19.1 (3.8-34.4)	17%
All Deaths[ǂ]	91 / 17.8	21.2 (15.8-26.6)	100%	55 / 9.0	108.4 (74.1-142.7)	100%

Absolute Excess Risks presented per 10,000 person-years. ǂ AER for all causes of death was 21.2 per 10,000 person-years prior to 30 years from diagnosis and 108.4 per 10,000 person-years poster 30 years from diagnosis, but due to rounding the specific causes of death sum to 21.4 and 108.8 respectively.

Table 2.5.4. SIRs and AERs for developing specific SPNs after Wilms' tumour

Outcome	Obs/Exp	SIR (95%CI)	AER (95%CI)[1]	AER (95%CI)[1], (N) < 30 Years from diagnosis	AER (95%CI)[1], (N) ≥ 30 Years from diagnosis
All	71/15.1	4.7 (3.7-5.9)	16.6 (11.7-21.5)	11.8 (7.4-16.1) (41)	44.6 (23.0-66.3) (30)
Digestive[2]	17/1.3	13.0 (7.6-20.9)	4.7 (2.3-7.1)	2.3 (0.5-4.1) (7)	18.2 (5.7-30.7) (10)
Genitourinary	9/3.5	2.6 (1.2-4.9)	1.6 (-0.1-3.4)	1.8 (0.0-3.6) (7)	0.5 (-5.1-6.1) (2)
Breast	9/2.9	3.1 (1.4-5.8)	1.8 (0.1-3.5)	1.5 (-0.4-1.8) (5)	3.3 (-4.6-11.2) (4)
Bone	6/0.3	20.6 (7.5-44.8)	1.7 (0.3-3.1)	1.6 (0.1-3.2) (5)	2.0 (-2.0-5.9) (1)

[1] indicates that AER is shown per 10,000 person – years. 30 other SPNs include: soft tissue sarcoma (6), unknown primary site (5), glioma (3), leukaemia (3), NHL (3), thyroid (3), melanoma (2), adrenal (1), Hodgkin's lymphoma (1), mesothelioma (1), leiomyosarcoma (1) and oral (1). [2]The 17 digestive SPNs comprise: Bowel (7), Retroperitoneum/Peritoneum (4), Liver (2), Pancreas (1), Small Intestine (1), Pyloric Antrum (1) and Unknown Digestive Site (1).

Table 2.5.5 Differences in mean SF–36 scores between Wilms' tumour survivors and OHLS reference population

SF-36 Scale	Difference in mean (95%CI)[1]
Reported Health Change	0.0 (–1.1, 1.1)
Physical Function	–1.8 (– 3.3, –0.9)
Role–Physical	–1.2 (–3.3, 0.9)
Role–Emotional	3.4 (1.2, 5.6)
Social Functioning	–0.1 (-1.4, 1.3)
Mental Health	0.6 (–0.6, 1.8)
Vitality	0.0 (–1.4, 1.4)
Bodily Pain	0.3 (–1.2, 1.9)
General Health Perception	–6.7 (–8.1, –5.2)

[1] Calculated scores were adjusted for age and sex.

Table 2.5.6 Odds Ratios (ORs) of pregnancy outcomes, smoking status, alcohol consumption, education level, marriage status and hospitalisation of Wilms' Tumour Survivors.

	Proportion of Affected Outcomes (%)	OR (95%CI)
Pregnancy outcome[1]		
Females Survivors		
Low Birth Weight	61 / 412 (14.8%)	3.3 (2.2, 4.9)
Premature	66 / 412 (16.0%)	3.1 (2.1, 4.7)
Miscarriage	67 / 412 (16.3%)	1.4 (0.9, 2.1)
Partners of Males Survivors		
Low Birth Weight	11 / 235 (4.7%)	0.7 (0.4, 1.5)
Premature	15 / 235 (6.4%)	0.6 (0.3, 1.3)
Miscarriage	34 / 235 (14.5%)	1.2 (0.7, 1.9)
Smoking[2]		
Current Regular Smoker	220 / 934 (23.6%)	0.7 (0.6, 0.8)
Alcohol[3]		
Alcohol Consumption	766 / 942 (81.3%)	0.7 (0.6, 0.9)
Consumption Over Recommendation	210 / 766 (27.4%)	0.8 (0.7, 1.0)
Consuming Harmful Doses	34 / 766 (4.4%)	0.5 (0.3, 0.7)
Education (Achievement)[4]		
Degree	133 / 672 (19.8%)	0.9 (0.7, 1.1)
Teaching Qualification	204 / 672 (30.4%)	0.9 (0.7, 1.1)
A–level	385 / 774 (49.8%)	0.9 (0.8, 1.1)
O–level	690 / 924 (74.7%)	1.0 (0.8, 1.1)
Marital status[5]		
Males	123 / 426 (28.9%)	0.7 (0.5, 0.9)
Females	197 / 505 (39.0%)	1.0 (0.8, 1.3)
Hospitalisations[6]		
Talked to a doctor in the last 2 weeks	152 / 900 (16.9%)	1.2 (1.0,1.5)
Not on long-term follow up	88 / 549 (16.0%)	1.1 (0.9,1.4)
On long-term follow up	57 / 329 (17.3%)	1.3 (1.0,1.8)
Attended Hospital Outpatient	229 / 897 (25.5%)	2.6 (2.2,3.1)
Not on long-term follow up	123 / 546 (22.5%)	2.1 (1.7,2.6)
On long-term follow up	101 / 329 (30.7%)	3.5 (2.7,4.6)
Hospitalised as a Day Patient	118 / 904 (13.1%)	1.7 (1.3,2.1)
Not on long-term follow up	71 / 552 (12.9%)	1.5 (1.1,2.0)
On long-term follow up	43 / 330 (13.0%)	1.9 (1.3,2.7)
Hospitalised as an Inpatient	93 / 904 (10.3%)	2.0 (1.6,2.6)
Not on long-term follow up	55 / 553 (10.0%)	1.9 (1.4,2.6)
On long-term follow up	36 / 329 (10.9%)	2.3 (1.6,3.5)

Total numbers represent the number of Wilms' Tumour survivors that answered a question relating to the specific outcome on the BCCSS questionnaire or in the case of pregnancies, the total number of pregnancies in female survivors of Wilms' Tumour.

[1] pregnancies of WT survivors who received abdominal radiotherapy versus pregnancies of survivors of any other childhood cancer who did not receive abdominal radiotherapy.

[2] adjusted for sex, attained age, marital status, socioeconomic classification, level of educational attainment.

[3] controlled for attained age, gender, legal marital status, socioeconomic classifications, educational attainment, and region, and took into account the GHS weighting factor, for the likelihood of consuming over the recommendations for weekly alcohol units or consuming harmful weekly amounts of alcohol.

[4] adjusted for, sex and attained age.

[5] compared to British population marriage statistics from ONS 2002.

[6] versus never compared to the general British population.

Table 2.5.7. Results of a comprehensive review, using hospital records and autopsy reports, of 25* causes of death relating to the 25 deaths coded as cardiac on the death certificate.

Type of Circulatory Death	Frequency	Comments
Myocardial Infarction	9	4 had chest radiotherapy and/or lung metastasis documented.
Cardiac Failure	7	6 had chest radiotherapy documented, 2 also had renal failure. Myocardial, lung and liver fibrosis at autopsy in 2.
Pulmonary Embolism	3	
Other	2	Comprises 1 atrial myxoma, 1 alcoholic cardiomyopathy.

*4 were considered deaths due to renal failure. The age of death was over 50 years in only 4 persons.

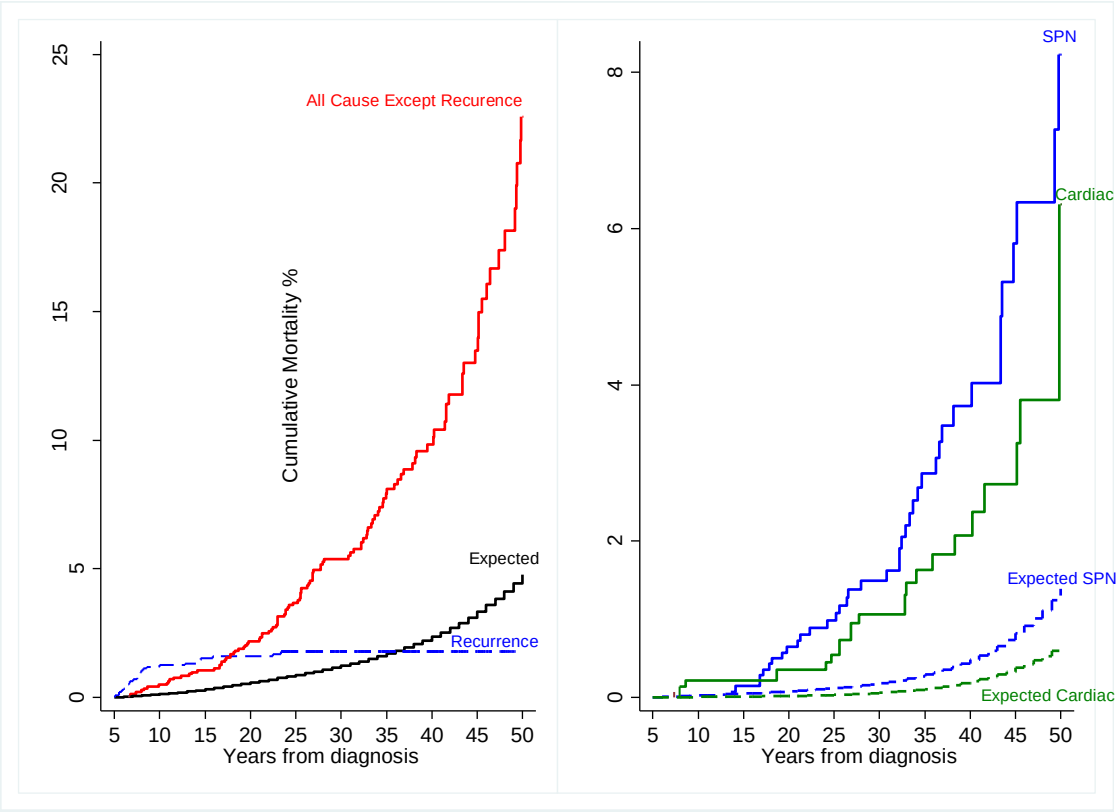


Figure 2.5.1 Observed and expected cumulative mortality among 1,441 survivors of childhood Wilms' tumour.

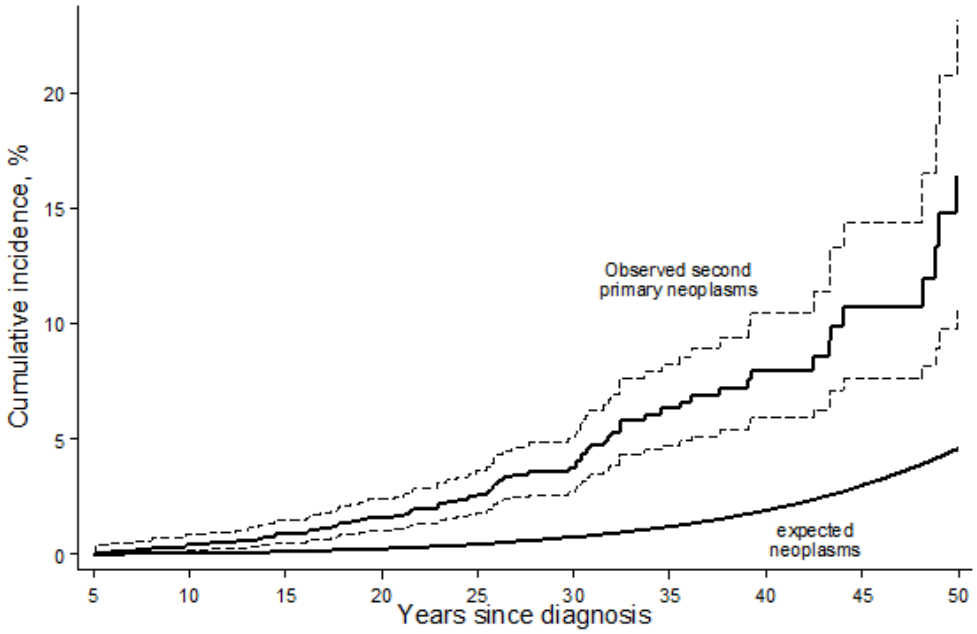


Figure 2.5.2 Observed and expected cumulative incidence of developing a SPN among 1,441 survivors of Wilms' tumour with 95% Confidence Intervals

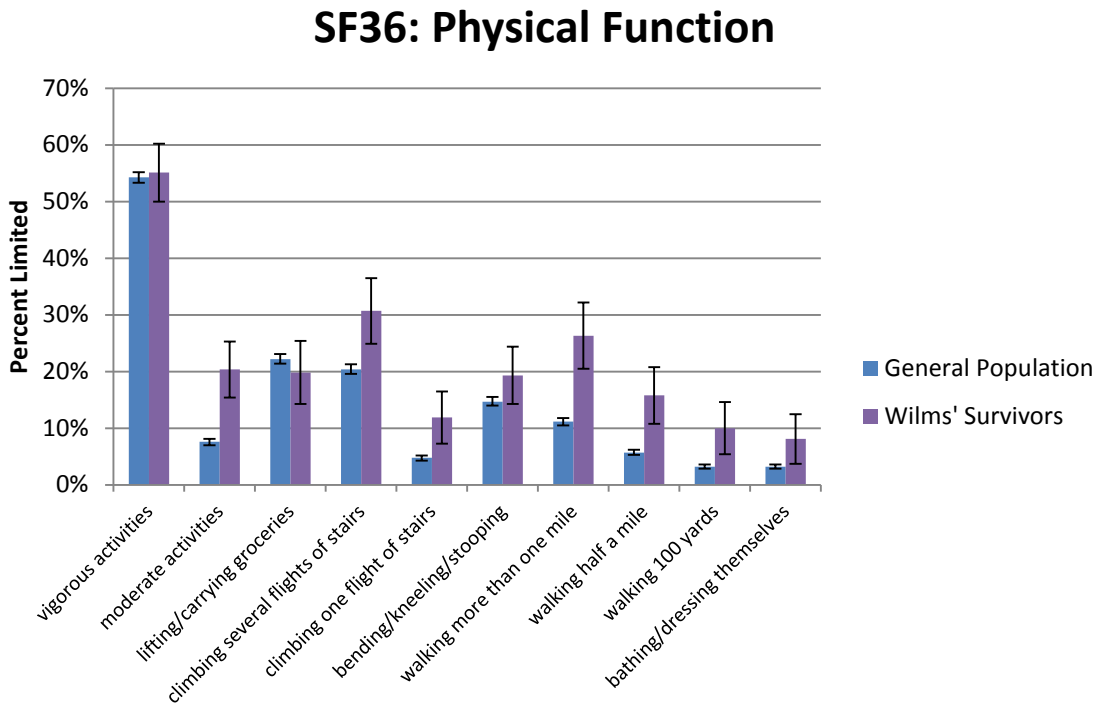


Figure 2.5.3 Specific questions underlying the SF36 Physical Function scale – directly standardised proportions with limitation in specific activities.

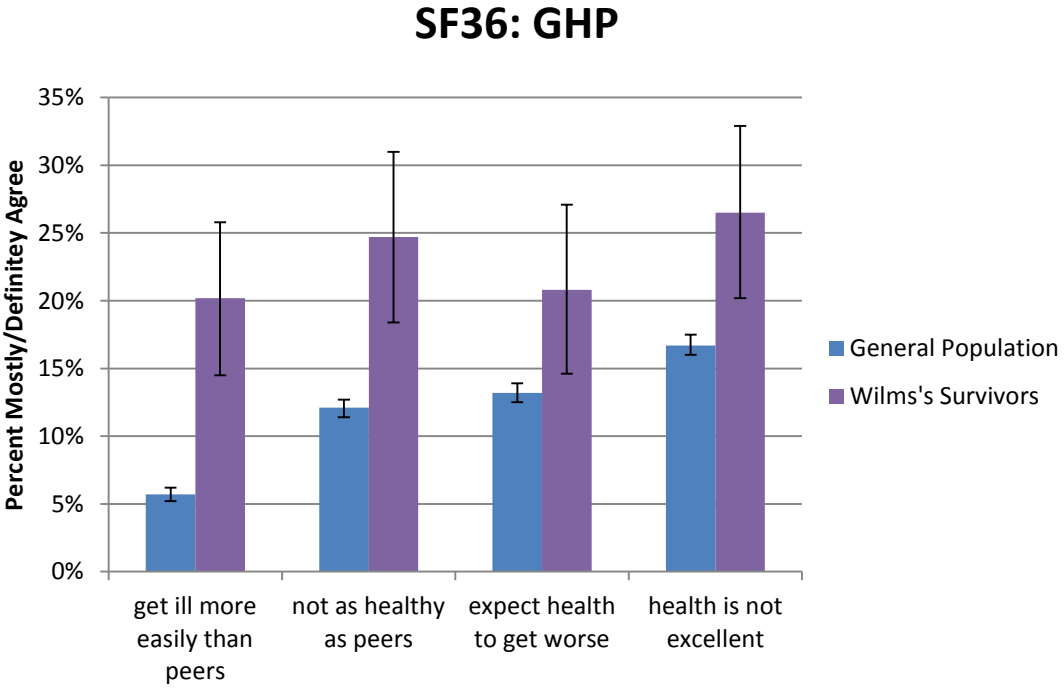


Figure 2.5.4 Specific questions underlying the SF36 General Health Perception scales – directly standardised proportions with specified level of agreement in relation to each question.

3 LONG-TERM RENAL MORBIDITY IN SURVIVORS OF CHILDHOOD CANCER IN THE BRITISH CHILDHOOD CANCER SURVIVOR STUDY USING DATA FROM THE NATIONAL HOSPITAL EPISODE STATISTICS.

Abstract

Background: Survivors of childhood cancer are at risk of renal conditions occurring many years after their childhood cancer diagnosis. However, no large-scale study has yet to investigate the risk of hospitalisation due to specific renal diseases. We investigated the risks of hospitalisation due to specific renal diseases among five-year survivors of childhood cancer.

Methods: The British Childhood Cancer Survivor Study includes 34,489 five-year survivors of childhood cancer. We measured the risk of hospitalisation due to glomerular disease (i.e. excess blood and protein in the urine), renal tubulo-interstitial disease (i.e. inflammation of the kidneys affecting interstitial area surrounding the tubules), renal failure (i.e. kidneys failing to filter waste products from the blood which is measured by the glomerular filtration rate), urolithiasis (i.e. kidney stones), urinary tract infection, other kidney disorders and other urinary system diseases by type of childhood cancer, gender, age at cancer diagnosis, year of cancer diagnosis and attained age of the hospitalisation.

Results: Risk of being hospitalised due to a renal condition was 2-fold expected for survivors compared to the general population with nearly 1 excess hospitalisation per 500 survivors per year. Survivors of neuroblastoma (4-fold), Wilms' Tumour (3-fold) and soft tissue sarcoma (3-fold) experienced the highest excess risks of renal morbidities with 45, 37 and 41 excess hospitalisations per 10,000 survivors per year respectively. Survivors of Wilms' tumour had a 30-fold risk of being hospitalised for chronic renal failure and a 15-fold risk of being hospitalised for acute renal failure compared to the general population.

Conclusion: Survivors of childhood cancer are at twice the risk of being hospitalised due to any renal disease compared to the general population. Specific risks were highest for survivors of Wilms' tumour whom had a 30-fold risk of being hospitalised due to chronic renal failure compared to the general population. Monitoring of glomerular filtration rate (GFR) levels in survivors of Wilms' tumour is advisable, especially in those who are aged 5-29.

3.1 Introduction

Five-year survival after childhood cancer has improved, over recent decades, to approximately 80% among those diagnosed between 2000 and 2007[4]. Although survival rates are increasing, survivors ,particularly of Wilms' tumour (WT), are at risk of a range of renal related morbidities such as acute and chronic renal failure[175]. A previous study relating to survivors of non-Hodgkin's lymphoma (NHL), found that survivors were at higher risk of glomerular disease[176] with a third of the survivors exhibiting proteinuria, and at a 34% increased risk of renal failure and survivors experienced significantly decreased glomerular filtration rates[7,69-71,177,178]. Other studies showed that survivors of childhood cancer who receives Cisplatin, Carboplatin, high-dose Cyclophosphamide, nephrectomy and abdominal radiation also had an increased risk of developing renal disease[70,100,179].

However, these studies focused on all childhood cancer survivors or survivors of specific diagnoses rather than survivors who were exposed to specific risk exposures. The majority of previous studies had fewer than 50 observed renal events which were insufficient to satisfactorily address the risks of renal diseases. No previous large-scale study has investigated the risks of renal tubulo-interstitial disease, urolithiasis and acute renal failure in survivors of childhood cancer.

To our knowledge, this is the first study to analyse the risk of hospitalisation due to long-term renal morbidities in five-year survivors of childhood cancer in a UK population-based environment. The main advantage of this current study – in addition to being large-scale and population-based – is that 60% of the cohort, who were born at least 25 years from the date of exit, survived for at least 25 years from

the date of their first primary neoplasm diagnosis (FPN) indicating a large pool of survivors still on follow-up.

The principal objective of this study was to investigate risk of hospitalisation due to long-term renal morbidities among five-year survivors of childhood cancer, specifically: (1) glomerular disease (i.e. excess blood and protein in the urine), (2) renal tubulo-interstitial disease (i.e. inflammation of the kidneys affecting interstitial area surrounding the tubules), (3) renal failure (i.e. kidneys failing to filter waste products from the blood which is measured by the glomerular filtration rate), (4) urolithiasis (i.e. kidney stones), (5) urinary tract infection, (6) other kidney disorders and (7) other urinary system diseases.

3.2 Methods

British Childhood Cancer Survivor Study (BCCSS)

The British Childhood Cancer Survivor Study (BCCSS) is a large-scale population based cohort study established to investigate adverse health and social outcomes of childhood cancer and its treatment. The BCCSS includes 34,489 five-year survivors of childhood cancer who were diagnosed before 15 years of age, between 1940 and 2006 in Britain. Of these, 27,976 five-year survivors remained at risk after the period at which the Hospital Episode Statistics (HES) began (1st April 1997). The BCCSS cohort was ascertained through the population-based National Registry of Childhood Tumours. Ascertainment of deaths (including underlying cause of death) in the BCCSS was achieved through flagging the entire cohort of childhood cancer survivors at the population-based Health and Social Care Information Centre

(HSCIC). Flagging informs the BCCSS when a survivor dies and provides linkage between the population-based cohort and the national population-based death and cancer registration systems.

Hospital Episode Statistics (HES)

The national Hospital Episode Statistics database records all in-patient hospital admissions, outpatients and A&E admission in NHS hospitals in England. The British Childhood Cancer Survivor Study was linked to HES to investigate the risks of hospitalisation due to renal morbidities—of those who were still alive when HES began (1st April 1997) 81% linkage to HES was achieved. In the cohort, 27,976 five-year survivors remained at risk after the date at which Hospital Episode Statistics (HES) were initiated (1st April 1997). We defined renal morbidities using codes from the International Classification of Diseases (Tenth Revision)[180], specifically; glomerular disease (ICD10: N00-N08), renal tubulo-interstitial disease (ICD10: N10-N16), renal failure (ICD10: N17-N19), urolithiasis (ICD10: N20-N23), urinary tract infection (ICD10: N39.0), other disorders of kidney and ureter (ICD10: N25-N29) and other diseases of the urinary system (ICD10: N30-N39, excluding N39.0) (see Appendix 8.3).

Statistical Analysis

Hospitalisation due to Renal Morbidities

To investigate hospitalisations, numbers of first observed hospitalisations due to all renal morbidities among all five-year childhood cancer survivors were compared with

the comparable number of expected hospitalisations from the general population. Secondary analyses investigated the numbers of first observed hospitalisations due to seven unique renal diseases among all five-year childhood cancer survivors and were compared with the comparable number of expected hospitalisations from the general population. Expected hospitalisations were calculated by using the rates of hospitalisation in the general population, population denominators were obtained from the Office for National Statistics (ONS), and indirectly standardised on the survivor cohort using the person-years from the numerator obtained from the survivor cohort. The period at risk began 1st April 1997 for those who were at least five-year survivors on this date, or date of becoming a five-year survivor if this was after 1st April 1997, and ended at the date of first occurrence of loss of follow up (N=294), death (N=1,953) or exit (31st December 2012) (N=25,729). Standardised hospitalisation ratios (SHR) for specific renal morbidities were calculated as the ratio of first observed hospitalisations over expected number of hospitalisations for each specific type of renal morbidity. Absolute excess risks (AER) were calculated by taking the number of observed first hospitalisations minus expected number of first hospitalisations divided by the number of person-years at risk multiplied by 10,000. An external Poisson regression model was performed to assess the risk of hospitalisations due to renal morbidities, by calculating relative risks (RR) and relative excess risks (RER), adjusting for possible risk factors. The model was adjusted for gender, specific categories of attained age, age of diagnosis, decade of diagnosis and type of childhood cancer.

Statistical significance for all analyses was defined as a 2-sided P<0.05. All analyses were carried out in Stata 13 (StataCorp, College Station, Texas).

3.3 Results

Cohort Characteristics

From the total of 27,976 five-year survivors of childhood cancer in the cohort, 1,183 (4.2%) had been hospitalised for a renal morbidity at least once. When analysing specific renal diseases, 28 (0.1%) survivors were admitted for glomerular disease, 206 (0.7%) for renal tubulo-interstitial disease, 172 (0.6%) for renal failure, 183 (0.7%) for urolithiasis, 481 (1.7%) for urinary tract infection, 48 (0.2%) for other disorders of the kidney and 375 (1.3%) for other urinary system diseases (Table 3.5.1). Total follow-up of five-year survivors, in relation to hospitalisations, was 308,612 person-years with mean and median follow-up of 11.1 and 13.2 years for the duration of HES (1997–2012) respectively.

Hospitalisations due to all Renal Morbidities

Overall, survivors experienced a 2-fold increased risk of being hospitalised for any renal morbidity (SHR=1.9; 95%CI: 1.8-2.0) with 18 excess hospitalisations per 10,000 person-years (AER=18.0; 95%CI: 15.8-20.2) compared to the general population (Table 3.5.2). Survivors who experienced the highest excess risk of renal morbidities were neuroblastoma (SHR=3.6; 95%CI: 2.9-4.4), Wilms' Tumour (SHR=2.9; 95%CI: 2.4-3.4) and soft tissue sarcoma (SHR=2.9; 95%CI: 2.4-3.5) with 45, 37 and 41 excess hospitalisations per 10,000 person-years respectively. After

adjustment for potential confounders, survivors of soft tissue sarcoma had the highest risk (RR=2.4; 95%CI: 2.0-3.0) compared to the reference group (i.e. leukaemia). Both males and females had an elevated risk of being hospitalised, 1.9-fold and 1.8-fold expected respectively, but females were significantly less likely to be hospitalised compared to males (RR=0.7; 95%CI: 0.6-0.8). Following 5-year survival, the excess risk of being hospitalised due to a renal disease (both RR and RER) decreased significantly with increasing attained age ($P < 0.01$).

Hospitalisations due to Glomerular Disease

Survivors of childhood cancer experienced an increased risk of hospitalisations due to glomerular disease (SHR=1.6; 95%CI: 1.1-2.3). When examining survivors by childhood cancer diagnosis, only survivors of Wilms' tumour (SHR=4.5; 95%CI: 2.0-9.9) and non-Hodgkin lymphoma (SHR=3.3; 95%CI: 1.1-10.2) were at an increased risk of being hospitalised for glomerular disease (Table 3.5.3). Females were significantly more likely than expected to be hospitalised due to a glomerular disease (SHR=2.1; 95%CI: 1.3-3.6).

Hospitalisations due to Renal Tubulo-Interstitial Disease

Overall, survivors had a 1.9-fold increased risk of being hospitalised for a renal tubulo-interstitial disease (SHR=1.9; 95%CI: 1.7-2.2) with 3.1 excess hospitalisations per 10,000 person-years (AER=3.1; 95%CI: 2.2-4.0). When examining by type of childhood cancer diagnosis, survivors of soft tissue sarcoma (SHR=5.4; 95%CI: 3.9-7.4), neuroblastoma (SHR=4.6; 95%CI: 3.0-7.1) and Wilms' tumour (SHR=3.7;

95%CI: 2.6-5.3) were at the highest multiplicative excess risk of being hospitalised for a renal tubule-interstitial disease (Table 3.5.4). These survivors also contributed the highest number of excess cases of hospitalisation due to renal tubulo-interstitial disease; neuroblastoma (AER=10.9; 95%CI: 4.8-17.0), Wilms' tumour (AER=9.2; 95%CI: 4.8-13.6) and soft tissue sarcoma (AER=14.3; 95%CI: 8.6-20.1). Compared to survivors of leukaemia, those who survived soft tissue sarcoma had the highest excess risk (RR=5.2; 95%CI: 3.0-8.9). Following 5-year survival, the excess risk of being hospitalised due to renal tubulo-interstitial disease (both RR and RER) decreased significantly with increasing attained age ($P < 0.01$).

Hospitalisations due to Renal Failure

Survivors had a 6-fold expected risk of being hospitalised due to renal failure (SHR=5.8; 95%CI: 5.0-6.7) with 4.6 excess hospitalisations per 10,000 person-years (AER=4.6; 95%CI: 3.8-5.4). Almost all first primary diagnosis groups had a significantly elevated excess risk – except non-Hodgkin's lymphoma (NHL) and non-heritable retinoblastoma survivors (Table 3.5.5). At highest excess risk were survivors of Wilms' tumour (SHR=21.8; 95%CI: 16.4-29.1), neuroblastoma (SHR=9.4; 95%CI: 5.1-17.5), bone (SHR=7.1; 95%CI: 3.8-13.2) and soft tissue sarcoma (SHR=8.5; 95%CI: 5.4-13.3). The highest excess number of hospitalisations were from survivors of Wilms' Tumour (AER=17.8; 95%CI: 12.4-23.2) and soft tissue sarcoma (AER=8.2; 95%CI: 4.0-12.3). Compared to survivors of Leukaemia, those who survived Wilms' tumour had the highest multiplicative excess risk (RR=6.7; 95%CI: 4.0-11.3). Both males and females had an elevated risk of being hospitalised (SHR=5.3; 95%CI: 4.6-6.4) and (SHR=6.8; 95%CI: 5.4-8.5) respectively. Following 5-

year survival, the excess risk of being hospitalised due to a renal failure (both RR and RER) decreased with increasing age ($P < 0.05$).

Of the 172 renal failures (Table 3.5.1), 37% were acute (N=64), 48% were chronic (N=82) and 15% were unknown (N=26). Survivors had a similar excess risk of being hospitalised for a chronic renal failure (SHR=6.4; 95%CI: 5.1-7.9) and acute renal failure (SHR=5.0; 95%CI: 3.9-6.4). Survivors of Wilms' tumour had the greatest multiplicative excess risk of being hospitalised for both chronic (SHR=29.6; 95%CI: 20.4-42.8) and acute (SHR=14.9; 95%CI: 8.7-25.7) renal failure. The number of excess cases of hospitalisations due to chronic renal failure and acute renal failure for survivors of Wilms' tumour was 10.9 (95%CI: 6.7-15.1) and 4.9 (95%CI: 2.0-7.7) respectively (Table 3.5.6, Table 3.5.7). Survivors of other childhood cancers also had increased risks, but not as high as Wilms' tumour survivors and also very few groups had increased excess numbers of hospitalisation compared to expected. Both males and females had significantly elevated risk of being hospitalised due to acute renal failure (SHR=4.8; 95%CI: 3.5-6.5) and (SHR=5.5; 95%CI: 3.6-8.2) and to chronic renal failure (SHR=5.6; 95%CI: 4.2-7.5) and (SHR=7.7; 95%CI: 5.6-10.6) respectively. Following 5-year survival, the multiplicative excess risk of being hospitalised due to both acute and chronic renal failure decreased with increasing age ($P < 0.001$).

Hospitalisations due to Urolithiasis

Overall, survivors were more likely to be hospitalised for urolithiasis than the general population (SHR=1.3; 95%CI: 1.1-1.5) and only survivors of neuroblastoma

(SHR=2.7; 95%CI: 1.6-4.7) and soft tissue sarcoma (SHR=2.3; 95%CI: 1.5-3.4) had elevated risk of being hospitalised for urolithiasis (Table 3.5.8). Following 5-year survival, the multiplicative excess risk of being hospitalised due to urolithiasis significantly decreased with increasing attained age ($P < 0.001$).

Hospitalisations due to Urinary Tract Infections

Survivors of childhood cancer experienced twice the risk of being hospitalised for urinary tract infection (SHR=2.2; 95%CI: 2.0-2.4) compared to the general population. Survivors of all types of childhood cancer, except for lymphomas and retinoblastomas, had a significantly increased risk of being hospitalised for urinary tract infection compared to the general population. This risk was highest for survivors of neuroblastoma (SHR=3.6; 95%CI: 2.6-5.0), CNS tumours (SHR=3.1; 95%CI: 2.7-3.7) and Wilms' tumour (SHR=3.0; 95%CI: 2.3-4.0) with 17, 16 and 14 excess hospitalisations per 10,000 survivors per year compared to the general population, respectively (Table 3.5.9). After adjusting for confounders, survivors of CNS tumours and bone tumours had the highest multiplicative excess risk (RR=1.9; 95%CI: 1.4-2.5) and (RR=1.9; 95%CI: 1.2-3.2) compared to survivors of leukaemia, respectively. Females were significantly less likely to be hospitalised for urinary tract infection compared to males (RR=0.7; 95%CI: 0.5-0.9). Following 5-year survival, the excess risk of being hospitalised due to urinary tract infection (both RR and RER) significantly decreased with increasing attained age ($P < 0.001$) and also significantly decreased for survivors who were diagnosed with their childhood cancer in more recent years ($P < 0.001$).

Hospitalisations due to Other Kidney Diseases

Survivors had a 6.5-fold excess risk of being hospitalised for other kidney conditions (SHR=6.5; 95%CI: 4.9-8.6), which include impaired renal tubular function (N=4), atrophy of kidney (N=3), small kidney (N=2), unspecified disorders (N=39). When examining survivors by their childhood cancer diagnosis, survivors of neuroblastoma (SHR=20.1; 95%CI: 9.0-44.8), Wilms' tumour (SHR=14.3; 95%CI: 7.1-28.6) and soft tissue sarcoma (SHR=13.3; 95%CI: 6.4-28.0) were the three groups with the highest excess risk of being hospitalised for other kidney diseases compared to the general population (Table 3.5.10). Compared to survivors of leukaemia, those who survived soft tissue sarcoma had the highest relative risk (RR=6.2; 95%CI: 1.6-23.6). Both males and females had an elevated risk of being hospitalised (SHR=5.5; 95%CI: 3.6-8.4) and (SHR=7.7; 95%CI: 5.2-11.3) respectively. Following 5-year survival, the multiplicative excess risk of being hospitalised due to other kidney diseases significantly decreased with increasing attained age (P = 0.006).

Hospitalisations due to Other Urinary System Diseases

Overall, survivors experienced a borderline statistically significant increased risk (SHR=1.1; 95%CI: 1.0-1.2) of being hospitalised for other urinary system diseases, which include cystitis (N=51), neuromuscular dysfunction of bladder (N=75), other disorders of bladder (N=78), complications of urethral system (N=96), proteinuria (N=1), incontinence (N=49) and other specified and unspecified disorders of the urinary system (N=25). Only survivors of CNS tumours, neuroblastoma and soft tissue sarcoma had significantly elevated risk of being hospitalised due to other

urinary system diseases; these were neuroblastoma (SHR=3.4; 95%CI: 2.5-4.5), soft tissue sarcoma (SHR=2.4; 95%CI: 1.8-3.1) and CNS (SHR=1.2; 95%CI: 1.0-1.5) with 23, 15 and 3 excess hospitalisations per 10,000 person-years respectively (Table 3.5.11). After adjusting for confounders, those who survived neuroblastoma and soft tissue sarcoma had the highest relative risk (RR=3.8; 95%CI: 2.5-5.6) and (RR=3.4; 95%CI: 2.3-5.0) compared to survivors of leukaemia, respectively. Females were significantly less likely to be hospitalised for other urinary system disease compared to males (RR=0.4; 95%CI: 0.3-0.5). Following 5-year survival, the multiplicative excess risk of being hospitalised due to other urinary system disease significantly decreased with increasing attained age ($P < 0.001$).

3.4 Discussion

To our knowledge, this is the first study that identifies the increased risk of hospitalisation due to specific renal diseases of survivors of childhood cancer in a large-scale population-based cohort. Overall, survivors had twice the risk of being hospitalised for any renal disease with nearly 1 extra hospitalisation per 500 survivors per year. This study demonstrated, for the first time, significantly elevated risks of hospitalisation due to any renal disease specifically for survivors of neuroblastoma, Wilms' tumour and soft tissue sarcoma. However, this risk significantly decreased with increasing attained age. Since the risk of hospitalisation due to renal disease is compared to the general population, the effect of decreasing risk with attained age may be due to the increasing risk of renal disease in the background population risk with older age – it may be possible to make potentially causal relationships for many, but not all, of these diseases.

Renal failure, which is considered to be one of the most important, and possibly fatal, renal morbidities was measured and survivors had a 6-fold risk of being hospitalised for this compared to the general population. In particular, survivors of Wilms' tumour had a 22-fold risk of being hospitalised due to renal failure with a corresponding excess of 18 cases compared to the general population per 10,000 survivors per year – previous studies demonstrated an elevated risk of renal failure in childhood cancer survivors but did not compare the risk to the general population and did not investigate the risk by childhood cancer diagnosis[7,69,175]. Previous studies have reported decreased glomerular filtration rate (GFR) due to anti-cancer therapy ultimately leading to chronic renal failure[70,178,179,181,182]– although we do not have information relating to treatment or GFR in this study, our survivors had a 6-fold risk

of being hospitalised for chronic renal failure compared to the general population. To our knowledge, no study has yet investigated acute renal failure as a long-term adverse effect following survival of childhood cancer in a large-scale population-based cohort. This study reports a 5-fold increased risk of childhood cancer survivors being hospitalised due to acute renal failure compared to the general population. Survivors of Wilms' tumour had a 15-fold increased risk of hospitalisation for acute renal failure with 1 excess case of hospitalisation per 2,000 survivors per year compared to the general population.

There have been very few studies investigating the onset of urolithiasis, or kidney stones, in survivors of childhood cancer. One particular US study found that the prevalence of kidney stones was twice as high in survivors than the general population for younger ages and approximately no difference in risk for survivors and the general population for older age groups[183]. In comparison, survivors aged 5–19 in our study had a 6-fold risk of being hospitalised for a kidney stone compared to the general population. This risk decreased to 2-fold for survivors aged 20–29, and survivors older than 30 no longer had a significantly elevated risk of being hospitalised for kidney stones compared to the general population. Although the US study had treatment data, they did not report on all childhood cancer types. Our study found that survivors of neuroblastoma and soft tissue sarcoma were the only childhood cancer types that actually had a significantly elevated risk of being hospitalised for kidney stones compared to the general population (3-fold and 2-fold risk respectively) – possibly because the majority of neuroblastoma and rhabdomyosarcoma, in children, occur in the abdomen.

We found no previous studies reporting hospitalisations due to other renal morbidities such as glomerular disease, renal tubulo-interstitial disease (or tubulo-interstitial nephritis), urinary tract infection, other kidney disorders and other urinary diseases after five-year childhood cancer survival. Our study shows that survivors of childhood cancer are, in fact, at an increased risk of being hospitalised due to these five renal conditions with approximately 2-fold risk of being hospitalised for glomerular disease, renal tubulo-interstitial disease, urinary tract infections, other urinary diseases and with a 6-fold increased risk of being hospitalised for other kidney diseases.

The increased risks of renal failure in survivors of childhood cancer indicate that survivors may need to be monitored for such diseases. The National Institute of Care and Excellence (NICE) guidelines for monitoring chronic renal failure[184], states that the frequency of recommended monitoring of GFR increases up to 4 times per year dependent on GFR levels, our study shows that survivors of childhood cancer are at increased risk of being hospitalised due to severe chronic renal failure (where GFR is an indicator of renal failure) compared to the general population. This indicates that it is important for survivors of childhood cancer to have their GFR frequently monitored – especially those who had WT and may already have kidney function impairment from the treatment or the cancer itself. However, measuring the GFR in all survivors of childhood cancer will require a lot of resources and in some cases the benefit of measuring GFR will not necessarily outweigh the cost (i.e. stress caused by frequently returning to the hospital for tests). Therefore, monitoring of GFR should only be considered for particular survivors who have a significantly high risk.

Limitations

A limitation of our study was that the HES database began from 1997 – this meant that no hospitalisation would have been recorded in the HES database prior to this time. As a result, survivors who were previously diagnosed with their initial cancer in 1940–1960 may have been hospitalised due to a renal condition after 30 years and this would be missed from the HES database. Therefore is likely that the risk of being hospitalised for those diagnosed in the early years is underestimated. It is difficult to determine how well validated HES data is in terms of accuracy of ICD coding and thus there may be overlap in some classifications of renal disease (such as renal tubulo-interstitial disease and impaired renal tubular function). Our study measures the hospitalisations due to renal conditions, which we assume that the renal condition has been ongoing and has eventually reached a stage where it becomes serious enough to hospitalise the survivor. However, survivors could have been hospitalised for renal diseases prior to 1997 and would not appear in this study, potentially underestimating the true risk of renal morbidities. Since our study includes patients diagnosed with cancer up until the end of 2006, five-year survival would potentially start in 2011 for these survivors. This would mean that those diagnosed with their initial cancer towards the end of the study (2000 onwards) may not accrue enough person-years to develop a renal disease or even be severe enough to be hospitalised for a renal disease indicating that hospitalisations due to renal disease would be severely underestimated for these survivors. Finally, the use of first hospitalisation may not capture the full extent of the disease and the disease may continue to recur in survivors over a prolonged period. Ideally, for a future study, repeated hospitalisations should be measured, to gauge the burden of the disease, but these hospitalisations should be validated. By doing this, it will be possible to investigate

the routes to certain diagnoses (i.e. chronic renal failure leading to acute renal failure after 10 years).

Conclusion

Survivors of childhood cancer are at twice the risk of being hospitalised due to a renal disease compared to the general population. Specific risks were highest for survivors of Wilms' tumour whom had a 30-fold risk of being hospitalised due to chronic renal failure compared to the general population. Monitoring of GFR levels in survivors of Wilms' tumour is strongly advised, especially in those who are aged 5-29, to help prevent severe cases of chronic renal failure from emerging.

3.5 Tables and Figures

Table 3.5.1 Characteristics of all 1,183 Renal Hospitalisations in the British Childhood Cancer Survivor Study.

		All Renal Hospitalisations (N = 1,183)
Sex	Male	504 (43%)
	Female	679 (57%)
Sub-types of Renal Morbidities[1]	Glomerular Disease	28
	Renal Tubulo-Interstitial	206
	Renal Failure	172
	Acute Renal Failure	64
	Chronic Renal Failure	82
	Urolithiasis	183
	Urinary Tract Infection	481
	Other Disorders of Kidney	48
	Other Urinary System	375
Age at Diagnosis of FPN (years)	Mean	6.3
	Median	5.2
	0 – 4	576 (48.7%)
	5 – 9	289 (24.4%)
	10 – 14	318 (26.9%)
Age at Renal Hospitalisation (years)[2]	Mean	27.9
	5 – 14	221 (18.7%)
	15 – 24	369 (31.2%)
	25 – 34	242 (20.5%)
	35 – 44	190 (16.0%)
	45 – 54	103 (8.7%)
	55 – 64	48 (4.1%)
	65+	10 (0.8%)
Decade of FPN diagnosis (years)[2]	Median	1986
	1940-1949	8 (0.7%)
	1950-1959	52 (4.4%)
	1960-1969	127 (10.7%)
	1970-1979	207 (17.5%)
	1980-1989	302 (25.5%)
	1990-1999	342 (28.9%)
	2000-2006	145 (12.3%)

[1] Sub-type of renal morbidities does not sum to the total number of renal hospitalisations as they were analysed as sub-groups and the outcome of interest changed for each time-to-event analysis. As a result, no percentages are shown as the numbers are not respective to the total.
[2] Skewed due to HES starting only in 1997 and renal events may have been missed prior to 1997 for some of the older survivors and hence lower numbers in the earlier years of childhood cancer diagnosis.

Table 3.5.2 Table of Standardised Hospitalisations Ratios due to renal disease compared to the general population.

	All Renal Outcomes				
	O/E	SHR	RR	AER	RER
Type of Childhood Cancer§					
Overall	1183 / 627.31	1.9 (1.8-2.0)	NA‡	18.0 (15.8-20.2)	NA‡
Leukaemia	252 / 158.87	1.6 (1.4-1.8)	REF	10.3 (6.9-13.8)	REF
Hodgkin's Lymphoma	52 / 46.35	1.1 (0.9-1.5)	1.1 (0.8-1.5)	2.8 (-4.2-9.7)	1.1 (0.8-1.6)
NHL	38 / 30.92	1.2 (0.9-1.7)	1.1 (0.8-1.6)	4.7 (-3.3-12.8)	1.1 (0.8-1.6)
CNS	296 / 147.52	2.0 (1.8-2.2)	1.6 (1.3-1.9)	21.9 (16.9-26.9)	1.6(1.3-1.9)
Neuroblastoma	87 / 24.20	3.6 (2.9-4.4)	2.1 (1.7-2.7)	45.1 (32.0-58.3)	2.2 (1.7-2.8)
N-Retinoblastoma	21 / 24.56	0.9 (0.6-1.3)	0.8 (0.5-1.2)	-3.2 (-11.2-4.9)	0.7 (0.4-1.2)
H-Retinoblastoma	14 / 16.59	0.8 (0.5-1.4)	0.7 (0.4-1.3)	-3.4 (-13.0-6.2)	0.7 (0.4-1.4)
Wilms' tumour	136 / 47.40	2.9 (2.4-3.4)	2.2 (1.8-2.7)	36.9 (27.4-46.4)	2.3 (1.8-2.8)
Bone	56 / 26.90	2.1 (1.6-2.7)	2.0 (1.5-2.8)	27.1 (13.4-40.8)	2.1 (1.5-2.9)
STS	123 / 42.11	2.9 (2.4-3.5)	2.4 (2.0-3.0)	40.8 (29.9-51.8)	2.6 (2.1-3.2)
Other	108 / 61.90	1.7 (1.4-2.1)	1.4 (1.1-1.8)	16.5 (9.2-23.8)	1.4 (1.1-1.8)
P-*Heterogeneity*†			< 0.001		< 0.001
Gender					
Male	504 / 259.31	1.9 (1.8-2.1)	REF	14.5 (11.9-17.1)	REF
Female	679 / 368.00	1.8 (1.7-2.0)	0.7 (0.6-0.8)	22.2 (18.6-25.9)	1.6 (1.4-1.8)
P-*Heterogeneity*†			< 0.001		< 0.001
Attained Age					
5-19	400 / 105.78	3.8 (3.4-4.2)	REF	28.6 (24.8-32.4)	REF
20-29	335 / 205.63	1.6 (1.5-1.8)	0.4 (0.3-0.4)	13.5 (9.7-17.2)	0.7 (0.6-0.8)
30-39	203 / 141.46	1.4 (1.3-1.6)	0.4 (0.3-0.4)	10.3 (5.6-14.9)	0.7 (0.6-0.8)
40-49	143 / 103.05	1.4 (1.2-1.6)	0.3 (0.2-0.3)	12.0 (5.0-19.0)	0.6 (0.5-0.8)
50+	102 / 71.40	1.4 (1.2-1.7)	0.2 (0.2-0.3)	18.4 (6.5-30.4)	0.7 (0.5-0.9)
P-*Trend*†			< 0.001		< 0.001
Age (Diagnosis)					
0 – 4	576 / 252.83	2.3 (2.1-2.5)	REF	22.2 (19.0-25.4)	REF
5 – 9	289 / 166.88	1.7 (1.5-1.9)	0.9 (0.7-1.0)	14.9 (10.9-19.0)	0.9 (0.8-1.1)
10 – 14	318 / 207.59	1.5 (1.4-1.7)	0.9 (0.8-1.1)	13.6 (9.3-17.9)	1.1 (0.9-1.3)
P-*Trend*†			0.356		0.634
Year (Diagnosis)					
1940 – 1969	187 / 124.99	1.9 (1.3-1.7)	REF	17.5 (9.9-25.1)	REF
1970 – 1979	207 / 139.95	1.5 (1.3-1.7)	1.1 (0.9-1.3)	12.0 (7.0-17.1)	0.8 (0.6-1.0)
1980 – 1989	302 / 170.24	1.8 (1.6-2.0)	1.3 (1.1-1.5)	15.5 (11.5-19.5)	0.8 (0.6-0.9)
1990 – 1999	342 / 153.62	2.2 (2.0-2.5)	1.1 (0.9-1.3)	18.5 (15.0-22.1)	0.6 (0.5-0.7)
2000 – 2006	145 / 38.50	3.8 (3.2-4.4)	1.0 (0.8-1.2)	34.5 (26.9-42.2)	0.3 (0.3-0.4)
P-*Trend*†			0.852		< 0.001

‡Not applicable for overall estimates.

†Not applicable for SHR and AER as these estimates were not calculated using a model.

§Abbreviations: non-Hodgkin's lymphoma (NHL), Central Nervous System (CNS), non-heritable retinoblastoma (N-Retinoblastoma), heritable retinoblastoma (H-Retinoblastoma).

Table 3.5.3 Table of Standardised Hospitalisations Ratios due to glomerular disease compared to the general population.

	Glomerular Disease				
	O/E	SHR	RR	AER	RER
Type of Childhood Cancer§					
Overall	28 / 17.12	1.6 (1.1-2.3)	NA‡	0.4 (0.0-0.7)	NA‡
Leukaemia	6 / 4.40	1.4 (0.6-3.0)	NA*	0.2 (-0.3-0.7)	NA*
Hodgkin's lymphoma	0 / 1.31	0.0 (NA)	NA*	-0.6 (NA)	NA*
NHL	3 / 0.92	3.3 (1.1-10.2)	NA*	1.4 (-0.9-3.6)	NA*
CNS	4 / 4.02	1.0 (0.4-2.7)	NA*	-0.0 (-0.6-0.6)	NA*
Neuroblastoma	1 / 0.78	1.3 (0.2-9.1)	NA*	0.2 (-1.2-1.5)	NA*
N-Retinoblastoma	2 / 0.70	2.9 (0.7-11.5)	NA*	1.1 (-1.3-3.6)	NA*
H-Retinoblastoma	0 / 0.50	0 (NA)	NA*	-0.6 (NA)	NA*
Wilms' tumour	6 / 1.35	4.5 (2.0-9.9)	NA*	1.9 (-0.1-3.8)	NA*
Bone	2 / 0.68	3.0 (0.7-11.8)	NA*	1.2 (-1.3-3.7)	NA*
STS	3 / 1.22	2.5 (0.8-7.6)	NA*	0.9 (-0.8-2.5)	NA*
Other	1 / 1.62	0.6 (0.1-4.4)	NA*	-0.2 (-0.9-0.5)	NA*
P-*Heterogeneity*†					
Gender					
Male	14 / 10.92	1.3 (0.8-2.2)	NA*	0.2 (-0.2-0.6)	NA*
Female	14 / 6.58	2.1 (1.3-3.6)	NA*	0.5 (0.0-1.0)	NA*
P-*Heterogeneity*†					
Attained Age					
5-19	15 / 4.80	3.1 (1.9-5.2)	NA*	1.0 (0.3-1.7)	NA*
20-29	5 / 4.27	1.1 (0.5-2.8)	NA*	0.1 (-0.4-0.5)	NA*
30-39	3 / 3.54	0.8 (0.3-2.6)	NA*	-0.1 (-0.6-0.5)	NA*
40-49	3 / 2.72	1.1 (0.4-3.4)	NA*	0.1 (-0.9-1.1)	NA*
50+	2 / 2.17	0.9 (0.2-3.7)	NA*	-0.1 (-1.7-1.5)	NA*
P-*Trend*†					
Age (Diagnosis)					
0 – 4	14 / 7.87	1.8 (1.1-3.0)	NA*	0.4 (-0.1-0.9)	NA*
5 – 9	8 / 4.49	1.8 (0.9-3.6)	NA*	0.4 (-0.2-1.1)	NA*
10 – 14	6 / 5.15	1.2 (0.5-2.6)	NA*	0.1 (-0.5-0.7)	NA*
P-*Trend*†					
Year (Diagnosis)					
1940 – 1969	5 / 3.70	1.4 (0.6-3.2)	NA*	0.4 (-0.8-1.6)	NA*
1970 – 1979	4 / 3.67	1.1 (0.4-2.9)	NA*	0.1 (-0.6-0.7)	NA*
1980 – 1989	2 / 4.34	0.5 (0.1-1.8)	NA*	-0.3 (-0.6-0.0)	NA*
1990 – 1999	12 / 4.42	2.7 (1.5-4.8)	NA*	0.7 (0.1-1.4)	NA*
2000 – 2006	5 / 1.36	3.7 (1.5-8.8)	NA*	1.2 (-0.2-2.6)	NA*
P-*Trend*†					

‡Not applicable for overall estimates.
†Not applicable for SHR and AER as these estimates were not calculated using a model.
*External Poisson regression models did not converge due to low overall numbers (N=28).
§Abbreviations: non-Hodgkin's lymphoma (NHL), Central Nervous System (CNS), non-heritable retinoblastoma (N-Retinoblastoma), heritable retinoblastoma (H-Retinoblastoma).

Table 3.5.4 Table of Standardised Hospitalisations Ratios due to renal tubulo-interstitial disease compared to the general population.

	Renal Tubulo-Interstitial Disease				
	O/E	SHR	RR	AER	RER
Type of Childhood Cancer§					
Overall	206 / 107.4	1.9 (1.7-2.2)	NA‡	3.1 (2.2-4.0)	NA‡
Leukaemia	36 / 32.00	1.1 (0.8-1.6)	REF	0.4 (-0.8-1.7)	REF
Hodgkin's lymphoma	12 / 6.35	1.9 (1.1-3.3)	2.0 (0.9-4.4)	2.8 (-0.6-6.1)	2.3 (1.0-5.4)
NHL	6 / 4.50	1.3 (0.6-3.0)	1.6 (0.6-4.1)	1.0 (-2.2-4.2)	1.7 (0.6-4.9)
CNS	29 / 24.37	1.2 (0.8-1.7)	1.0 (0.6-1.8)	0.7 (-0.9-2.2)	1.0 (0.5-1.9)
Neuroblastoma	20 / 4.37	4.6 (3.0-7.1)	2.5 (1.2-5.1)	10.9 (4.8-17.0)	2.6 (1.2-5.5)
N-Retinoblastoma	3 / 3.63	0.8 (0.3-2.6)	1.1 (0.3-3.5)	-0.6 (-3.6-2.4)	1.1 (0.3-4.2)
H-Retinoblastoma	2 / 2.27	0.9 (0.2-3.5)	1.2 (0.3-4.9)	-0.3 (-3.9-3.2)	1.1 (0.2-6.3)
Wilms' tumour	31 / 8.30	3.7 (2.6-5.3)	3.6 (2.0-6.2)	9.2 (4.8-13.6)	3.9 (2.1-7.1)
Bone	9 / 4.30	2.1 (1.1-4.0)	2.6 (1.1-6.1)	4.3 (-1.1-9.7)	2.8 (1.1-7.0)
STS	36 / 6.72	5.4 (3.9-7.4)	5.2 (3.0-8.9)	14.3 (8.6-20.1)	5.9 (3.3-10.6)
Other	22 / 10.58	2.1 (1.4-3.2)	2.0 (1.1-3.7)	4.0 (0.8-7.2)	2.1 (1.1-4.1)
P-*Heterogeneity*†			< 0.001		< 0.001
Gender					
Male	73 / 24.98	2.9 (2.3-3.7)	REF	2.8 (1.8-3.8)	REF
Female	133 / 82.42	1.6 (1.4-1.9)	0.6 (0.4-0.8)	3.5 (2.0-5.1)	2.7 (1.9-3.9)
P-*Heterogeneity*†			0.027		< 0.001
Attained Age					
5-19	103 / 24.11	4.3 (3.5-5.2)	REF	7.6 (5.7-9.5)	REF
20-29	54 / 48.32	1.1 (0.9-1.5)	0.5 (0.3-0.7)	0.6 (-0.9-2.1)	0.9 (0.6-1.4)
30-39	31 / 19.31	1.6 (1.1-2.3)	0.3 (0.2-0.6)	1.9 (0.1-3.7)	0.5 (0.3-0.9)
40-49	13 / 9.97	1.3 (0.8-2.2)	0.3 (0.1-0.5)	0.9 (-1.2-3.0)	0.4 (0.2-0.8)
50+	5 / 5.69	0.9 (0.4-2.1)	0.1 (0.1-0.3)	-0.4 (-2.9-2.1)	0.2 (0.1-0.7)
P-*Trend*†			< 0.001		< 0.001
Age (Diagnosis)					
0 – 4	112 / 45.61	2.5 (2.0-3.0)	REF	4.5 (3.1-5.9)	REF
5 – 9	39 / 29.23	1.3 (1.0-1.8)	0.6 (0.4-1.0)	1.2 (-0.3-2.6)	0.7 (0.4-1.2)
10 – 14	55 / 32.56	1.7 (1.3-2.2)	0.9 (0.6-1.5)	2.7 (1.0-4.5)	1.1 (0.7-1.8)
P-*Trend*†			0.640		0.883
Year (Diagnosis)					
1940 – 1969	23 / 10.01	2.3 (1.5-3.5)	REF	3.6 (1.0-6.2)	REF
1970 – 1979	29 / 17.30	1.7 (1.2-2.4)	1.3 (0.7-2.6)	2.1 (0.2-3.9)	1.3 (0.6-2.7)
1980 – 1989	58 / 33.13	1.8 (1.4-2.3)	1.7 (0.9-3.3)	2.9 (1.1-4.6)	1.8 (0.9-3.6)
1990 – 1999	70 / 37.39	1.9 (1.5-2.4)	1.2 (0.7-2.3)	3.2 (1.6-4.7)	1.4 (0.7-2.7)
2000 – 2006	26 / 9.57	2.7 (1.9-4.0)	1.0 (0.5-2.1)	5.3 (2.1-8.5)	0.7 (0.3-1.5)
P-*Trend*†			0.702		0.233

‡Not applicable for overall estimates.

†Not applicable for SHR and AER as these estimates were not calculated using a model.

§Abbreviations: non-Hodgkin's lymphoma (NHL), Central Nervous System (CNS), non-heritable retinoblastoma (N-Retinoblastoma), heritable retinoblastoma (H-Retinoblastoma).

Table 3.5.5 Table of Standardised Hospitalisations Ratios due to renal failure compared to the general population.

	Renal Failure				
	O/E	SHR	RR	AER	RER
Type of Childhood Cancer§					
Overall	172 / 29.61	5.8 (5.0-6.7)	NA‡	4.6 (3.8-5.4)	NA‡
Leukaemia	29 / 6.08	4.8 (3.3-6.9)	REF	2.5 (1.3-3.7)	REF
Hodgkin's lymphoma	7 / 2.60	2.7 (1.3-2.6)	1.4 (0.6-3.4)	2.1 (-0.4-4.7)	1.4 (0.6-3.4)
NHL	4 / 1.75	2.3 (0.9-6.1)	0.8 (0.2-2.7)	1.5 (-1.1-4.1)	0.8 (0.2-2.8)
CNS	28 / 7.32	3.8 (2.6-5.5)	1.3 (0.7-2.3)	3.0 (1.5-4.5)	1.3 (0.7-2.3)
Neuroblastoma	10 / 1.06	9.4 (5.1-17.5)	2.0 (0.9-4.7)	6.2 (1.9-10.5)	1.9 (0.8-4.4)
N-Retinoblastoma	0 / 1.28	0 (NA)	0 (NA)	-1.1 (NA)	0 (NA)
H-Retinoblastoma	3 / 0.88	3.4 (1.1-10.5)	1.2 (0.3-5.3)	2.7 (-1.6-7.1)	1.1 (0.2-5.6)
Wilms' tumour	46 / 2.11	21.8 (16.4-29.1)	6.7 (4.0-11.3)	17.8 (12.4-23.2)	7.0 (0.4-11.8)
Bone	10 / 1.40	7.1 (3.8-13.2)	3.4 (1.5-7.5)	7.8 (2.2-13.5)	3.4 (1.5-7.7)
STS	19 / 2.24	8.5 (5.4-13.3)	2.2 (1.1-4.5)	8.2 (4.0-12.3)	2.2 (1.0-4.5)
Other	16 / 2.89	5.5 (3.4-9.0)	1.9 (0.9-3.7)	4.6 (1.8-7.4)	1.9 (1.0-3.8)
P-*Heterogeneity*†			< 0.001		< 0.001
Gender					
Male	99 / 18.85	5.3 (4.3-6.4)	REF	4.7 (3.5-5.8)	REF
Female	73 / 10.76	6.8 (5.4-8.5)	1.3 (0.9-1.9)	4.3 (3.2-5.5)	0.7 (0.5-1.1)
P-*Heterogeneity*†			0.389		0.095
Attained Age					
5-19	76 / 3.59	21.1 (16.9-26.5)	REF	7.0 (5.3-8.6)	REF
20-29	42 / 6.97	6.0 (4.5-8.2)	0.5 (0.3-0.7)	3.6 (2.3-4.9)	0.7 (0.4-1.0)
30-39	31 / 6.73	4.6 (3.2-6.5)	0.2 (0.1-0.4)	4.0 (2.2-5.7)	0.5 (0.3-0.9)
40-49	11 / 5.64	2.0 (1.1-3.5)	0.2 (0.1-0.3)	1.6 (-0.3-3.5)	0.6 (0.3-1.1)
50+	12 / 6.67	1.8 (1.0-3.2)	0.1 (0.0-0.2)	3.1 (-0.8-7.0)	0.7 (0.3-1.3)
P-*Trend*†			< 0.001		0.037
Age (Diagnosis)					
0 – 4	92 / 10.97	8.4 (6.8-10.3)	REF	5.5 (4.2-6.7)	REF
5 – 9	45 / 7.83	5.7 (4.3-7.7)	1.2 (0.8-1.9)	4.5 (2.9-6.1)	1.3 (0.8-2.0)
10 – 14	35 / 10.81	3.2 (2.3-4.5)	1.0 (0.6-1.7)	2.9 (1.5-4.3)	1.1 (0.6-1.9)
P-*Trend*†			0.915		0.608
Year (Diagnosis)					
1940 – 1969	26 / 9.61	2.7 (1.8-4.0)	REF	4.5 (1.8-7.3)	REF
1970 – 1979	39 / 7.10	5.5 (4.0-7.5)	2.4 (1.3-4.2)	5.6 (3.5-7.8)	1.1 (0.6-2.0)
1980 – 1989	34 / 6.86	5.0 (3.5-6.9)	2.3 (1.3-4.1)	3.1 (1.8-4.4)	0.7 (0.4-1.3)
1990 – 1999	49 / 4.89	10.0 (7.6-13.3)	4.0 (2.3-6.9)	4.3 (2.9-5.6)	0.8 (0.5-1.4)
2000 – 2006	24 / 1.15	21.0 (14.0-31.3)	3.6 (1.9-6.8)	7.3 (4.3-10.4)	0.5 (0.3-1.0)
P-*Trend*†			< 0.001		0.016

‡Not applicable for overall estimates.
†Not applicable for SHR and AER as these estimates were not calculated using a model.
§Abbreviations: non-Hodgkin's lymphoma (NHL), Central Nervous System (CNS), non-heritable retinoblastoma (N-Retinoblastoma), heritable retinoblastoma (H-Retinoblastoma).

Table 3.5.6 Table of Standardised Hospitalisations Ratios due to acute renal failure compared to the general population.

	Acute Renal Failure				
	O/E	SHR	RR	AER	RER
Type of Childhood Cancer§					
Overall	64 / 12.77	5.0 (3.9-6.4)	NA‡	1.7 (1.2-2.2)	NA‡
Leukaemia	11 / 2.51	4.4 (2.4-7.9)	REF	0.9 (0.2-1.6)	REF
Hodgkin's lymphoma	4 / 1.14	3.5 (1.3-9.3)	1.3 (0.4-4.3)	1.4 (-0.5-3.3)	1.2 (0.4-4.4)
NHL	1 / 0.78	1.3 (0.2-9.1)	0.4 (0.1-3.5)	0.1 (-1.1-1.4)	0.4 (0.1-3.8)
CNS	14 / 3.20	4.4 (2.6-7.4)	1.4 (0.6-3.0)	1.6 (0.5-2.6)	1.2 (0.5-2.8)
Neuroblastoma	2 / 0.44	4.5 (1.1-18.1)	1.3 (0.3-6.0)	1.1 (-0.8-3.0)	1.3 (0.3-6.0)
N-Retinoblastoma	0 / 0.55	0 (NA)	0 (NA)	-0.5 (NA)	0 (NA)
H-Retinoblastoma	1 / 0.37	2.7 (0.4-19.2)	1.1 (0.1-9.0)	0.8 (-1.7-3.3)	1.1 (0.1-9.3)
Wilms' tumour	13 / 0.87	14.9 (8.7-25.7)	4.6 (2.0-10.5)	4.9 (2.0-7.7)	4.6 (2.0-10.7)
Bone	3 / 0.64	4.7 (1.5-14.6)	1.8 (0.5-6.9)	2.1 (-0.9-5.2)	2.0 (0.5-7.5)
STS	7 / 0.99	7.0 (3.4-14.8)	2.4 (0.9-6.4)	2.9 (0.4-5.4)	2.5 (0.9-6.7)
Other	8 / 1.28	6.3 (3.1-12.5)	2.1 (0.8-5.4)	2.4 (0.4-4.3)	2.2 (0.9-5.7)
P-*Heterogeneity*†			0.011		0.011
Gender					
Male	40 / 8.40	4.8 (3.5-6.5)	REF	1.8 (1.1-2.6)	REF
Female	24 / 4.37	5.5 (3.6-8.2)	1.0 (0.6-1.7)	1.4 (0.7-2.0)	0.6 (0.4-1.1)
P-*Heterogeneity*†			0.842		0.084
Attained Age					
5-19	20 / 1.20	16.7 (10.8-25.9)	REF	1.8 (1.0-2.6)	REF
20-29	18 / 3.06	5.9 (3.7-9.3)	0.5 (0.3-1.1)	1.5 (0.7-2.4)	1.2 (0.6-2.5)
30-39	11 / 2.47	4.5 (2.5-8.0)	0.4 (0.2-0.9)	1.4 (0.3-2.4)	1.1 (0.5-2.6)
40-49	11 / 2.36	4.7 (2.6-8.4)	0.4 (0.2-0.8)	2.5 (0.6-4.4)	1.6 (0.7-3.8)
50+	4 / 3.68	1.1 (0.4-2.9)	0.2 (0.1-0.5)	0.2 (-2.1-2.5)	2.9 (1.2-6.8)
P-*Trend*†			< 0.001		0.028
Age (Diagnosis)					
0 – 4	25 / 4.52	5.5 (3.7-8.2)	REF	1.4 (0.7-2.0)	REF
5 – 9	23 / 3.36	6.8 (4.5-10.3)	1.5 (0.8-2.8)	2.4 (1.2-3.5)	1.6 (0.9-3.1)
10 – 14	16 / 4.89	3.3 (2.0-5.3)	0.9 (0.4-1.8)	1.3 (0.4-2.3)	1.0 (0.4-2.1)
P-*Trend*†			0.699		0.945
Year (Diagnosis)					
1940 – 1969	12 / 4.50	2.7 (1.5-4.7)	REF	2.1 (0.2-3.9)	REF
1970 – 1979	20 / 2.75	7.3 (4.7-11.3)	2.9 (1.4-6.1)	3.0 (1.5-4.6)	1.1 (0.5-2.3)
1980 – 1989	9 / 2.78	3.2 (1.7-6.2)	1.5 (0.6-3.6)	0.7 (0.0-1.4)	0.3 (0.1-0.9)
1990 – 1999	17 / 2.21	7.7 (4.8-12.4)	2.5 (1.2-5.4)	1.4 (0.6-2.2)	0.4 (0.2-0.9)
2000 – 2006	6 / 0.54	11.2 (5.0-24.9)	2.5 (0.9-6.9)	1.7 (0.2-3.3)	0.2 (0.1-0.6)
P-*Trend*†			0.064		< 0.001

‡Not applicable for overall estimates.
†Not applicable for SHR and AER as these estimates were not calculated using a model.
§Abbreviations: non-Hodgkin's lymphoma (NHL), Central Nervous System (CNS), non-heritable retinoblastoma (N-Retinoblastoma), heritable retinoblastoma (H-Retinoblastoma).

Table 3.5.7 Table of Standardised Hospitalisations Ratios due to chronic renal failure compared to the general population.

	Chronic Renal Failure				
	O/E	SHR	RR	AER	RER
Type of Childhood Cancer§					
Overall	82 / 12.83	6.4 (5.1-7.9)	NA‡	2.2 (1.6-2.8)	NA‡
Leukaemia	8 / 2.66	3.0 (1.5-6.0)	REF	0.6 (-0.0-1.2)	REF
Hodgkin's lymphoma	2 / 1.13	1.8 (0.4-7.1)	1.8 (0.4-8.7)	0.4 (-0.9-1.8)	1.7 (0.3-8.9)
NHL	3 / 0.74	4.1 (1.3-12.6)	3.3 (0.9-12.8)	1.5 (-0.7-3.7)	3.2 (0.8-13.0)
CNS	10 / 3.16	3.2 (1.7-5.9)	1.9 (0.8-5.0)	1.0 (0.1-1.9)	1.9 (0.7-5.0)
Neuroblastoma	6 / 0.47	12.9 (5.8-28.7)	4.5 (1.6-13.2)	3.8 (0.5-7.1)	4.2 (1.4-12.7)
N-Retinoblastoma	0 / 0.56	0 (NA)	0 (NA)	-0.5 (NA)	0 (NA)
H-Retinoblastoma	1 / 0.39	2.5 (0.4-18.0)	1.8 (0.2-14.8)	0.8 (-1.7-3.3)	1.6 (0.1-17.2)
Wilms' tumour	28 / 0.95	29.6 (20.4-42.8)	13.9 (6.2-30.9)	10.9 (6.7-15.1)	14.5 (6.4-32.8)
Bone	5 / 0.59	8.5 (3.5-20.4)	7.7 (2.4-24.9)	4.0 (0.0-8.0)	8.0 (2.4-26.7)
STS	11 / 0.95	11.6 (6.4-20.9)	7.8 (3.1-19.4)	4.9 (1.7-8.1)	8.0 (3.1-20.3)
Other	8 / 1.23	6.5 (3.2-13.0)	3.6 (1.3-9.6)	2.4 (0.4-4.3)	3.7 (1.3-10.3)
P-*Heterogeneity*†			< 0.001		< 0.001
Gender					
Male	45 / 8.01	5.6 (4.2-7.5)	REF	2.2 (1.4-2.9)	REF
Female	37 / 4.81	7.7 (5.6-10.6)	2.1 (1.3-3.3)	2.2 (1.4-3.1)	0.9 (0.6-1.4)
P-*Heterogeneity*†			0.002		0.690
Attained Age					
5-19	45 / 1.70	26.4 (19.7-35.4)	REF	4.2 (2.9-5.4)	REF
20-29	20 / 2.87	7.0 (4.5-10.8)	0.4 (0.3-0.8)	1.7 (0.9-2.6)	0.6 (0.3-1.0)
30-39	9 / 3.28	2.7 (1.4-5.3)	0.2 (0.1-0.4)	0.9 (-0.0-1.9)	0.4 (0.2-0.9)
40-49	4 / 2.60	1.5 (0.6-4.1)	0.1 (0.0-0.2)	0.4 (-0.7-1.6)	0.3 (0.1-0.8)
50+	4 / 2.37	1.7 (0.6-4.5)	0.1 (0.0-0.2)	0.9 (-1.3-3.2)	0.3 (0.1-1.0)
P-*Trend*†			< 0.001		0.001
Age (Diagnosis)					
0 – 4	52 / 4.87	10.7 (8.1-14.0)	REF	3.2 (2.2-4.1)	REF
5 – 9	14 / 3.40	4.1 (2.4-6.9)	0.7 (0.4-1.3)	1.3 (0.4-2.2)	0.7 (0.3-1.2)
10 – 14	16 / 4.56	3.5 (2.2-5.7)	1.0 (0.5-2.0)	1.4 (0.4-2.3)	0.9 (0.4-1.8)
P-*Trend*†			0.728		0.481
Year (Diagnosis)					
1940 – 1969	11 / 4.04	2.7 (1.5-4.9)	REF	1.9 (0.1-3.7)	REF
1970 – 1979	14 / 3.41	4.1 (2.4-6.9)	1.4 (0.6-3.1)	1.9 (0.6-3.1)	1.0 (0.4-2.3)
1980 – 1989	19 / 3.05	6.2 (4.0-9.8)	2.0 (0.9-4.2)	1.8 (0.9-2.8)	0.9 (0.4-2.0)
1990 – 1999	26 / 1.89	13.7 (9.4-20.2)	3.4 (1.7-6.9)	2.3 (1.4-3.3)	0.9 (0.4-2.0)
2000 – 2006	12 / 0.44	27.4 (15.6-48.2)	2.7 (1.2-6.5)	3.7 (1.5-5.9)	0.6 (0.3-1.4)
P-*Trend*†			< 0.001		0.270

‡Not applicable for overall estimates.

†Not applicable for SHR and AER as these estimates were not calculated using a model.

§Abbreviations: non-Hodgkin's lymphoma (NHL), Central Nervous System (CNS), non-heritable retinoblastoma (N-Retinoblastoma), heritable retinoblastoma (H-Retinoblastoma).

Table 3.5.8 Table of Standardised Hospitalisations Ratios due to urolithiasis compared to the general population.

	Urolithiasis				
	O/E	SHR	RR	AER	RER
Type of Childhood Cancer§					
Overall	183 / 142.50	1.3 (1.1-1.5)	NA‡	1.3 (0.5-2.2)	NA‡
Leukaemia	36 / 32.72	1.1 (0.8-1.5)	REF	0.4 (-0.9-1.6)	REF
Hodgkin's lymphoma	19 / 13.76	1.4 (0.9-2.2)	1.9 (1.0-3.6)	2.6 (-1.6-6.7)	2.1 (1.1-4.1)
NHL	13 / 8.82	1.5 (0.9-2.5)	1.8 (0.9-3.7)	2.8 (-1.9-7.4)	2.0 (0.9-4.2)
CNS	39 / 33.71	1.2 (0.8-1.6)	1.1 (0.7-1.9)	0.8 (-1.0-2.5)	1.1 (0.6-2.0)
Neuroblastoma	13 / 4.78	2.7 (1.6-4.7)	1.9 (0.9-4.3)	5.7 (0.8-10.6)	1.9 (0.8-4.5)
N-Retinoblastoma	4 / 5.28	0.8 (0.3-2.0)	0.9 (0.3-3.2)	-1.1 (-4.6-2.3)	0.8 (0.2-4.1)
H-Retinoblastoma	0 / 3.93	0 (NA)	0 (NA)	-5.1 (NA)	0 (NA)
Wilms' tumour	12 / 10.54	1.1 (0.6-2.0)	1.3 (0.6-2.7)	0.6 (-2.2-3.3)	1.4 (0.7-3.1)
Bone	8 / 6.19	1.3 (0.6-2.6)	1.9 (0.8-4.2)	1.6 (-3.4-6.7)	2.0 (0.8-4.6)
STS	23 / 10.12	2.3 (1.5-3.4)	2.2 (1.2-4.1)	6.3 (1.7-10.9)	2.5 (1.3-4.7)
Other	16 / 12.65	1.3 (0.8-2.1)	1.2 (0.6-2.3)	1.2 (-1.6-3.9)	1.1 (0.5-2.4)
P-*Heterogeneity*†			0.053		0.052
Gender					
Male	118 / 102.17	1.2 (1.0-1.4)	REF	0.9 (-0.3-2.2)	REF
Female	65 / 40.32	1.6 (1.3-2.1)	1.0 (0.7-1.5)	1.7 (0.6-2.8)	0.6 (0.4-0.9)
P-*Heterogeneity*†			0.679		0.021
Attained Age					
5-19	48 / 7.67	6.3 (4.7-8.3)	REF	3.9 (2.6-5.2)	REF
20-29	74 / 45.75	1.6 (1.3-2.0)	0.3 (0.2-0.5)	2.9 (1.2-4.6)	1.4 (0.5-2.3)
30-39	32 / 44.99	0.7 (0.5-1.0)	0.2 (0.1-0.4)	-2.1 (-3.9—0.3)	1.6 (0.9-2.7)
40-49	19 / 28.97	0.7 (0.4-1.0)	0.1 (0.1-0.3)	-2.9 (-5.4—0.4)	1.1 (0.6-2.2)
50+	10 / 15.11	0.7 (0.4-1.2)	0.1 (0.1-0.2)	-3.0 (-6.6-0.6)	1.0 (0.5-2.3)
P-*Trend*†			< 0.001		0.801
Age (Diagnosis)					
0 – 4	72 / 52.54	1.4 (1.1-1.7)	REF	1.3 (0.2-2.4)	REF
5 – 9	46 / 39.19	1.2 (0.9-1.6)	0.9 (0.6-1.4)	0.8 (-0.8-2.4)	1.0 (0.6-1.7)
10 – 14	65 / 50.77	1.3 (1.0-1.6)	1.1 (0.7-1.8)	1.7 (-0.2-3.6)	1.4 (0.8-2.2)
P-*Trend*†			0.517		0.225
Year (Diagnosis)					
1940 – 1969	32 / 30.83	1.0 (0.7-1.5)	REF	0.3 (-2.7-3.4)	REF
1970 – 1979	43 / 41.24	1.0 (0.8-1.4)	0.9 (0.5-1.5)	0.0 (-0.2-0.3)	0.8 (0.4-1.4)
1980 – 1989	55 / 42.74	1.3 (1.0-1.7)	0.9 (0.6-1.5)	1.4 (-0.3-3.1)	0.7 (0.4-1.2)
1990 – 1999	44 / 23.90	1.8 (1.4-2.5)	0.8 (0.5-1.3)	1.9 (0.7-3.2)	0.3 (0.2-0.6)
2000 – 2006	9 / 3.78	2.4 (1.2-4.6)	0.7 (0.3-1.5)	1.7 (-0.2-3.6)	0.1 (0.0-0.3)
P-*Trend*†			0.260		< 0.001

‡Not applicable for overall estimates.

†Not applicable for SHR and AER as these estimates were not calculated using a model.

§Abbreviations: non-Hodgkin's lymphoma (NHL), Central Nervous System (CNS), non-heritable retinoblastoma (N-Retinoblastoma), heritable retinoblastoma (H-Retinoblastoma).

Table 3.5.9 Table of Standardised Hospitalisations Ratios due to urinary tract infection compared to the general population.

	Urinary Tract Infection				
	O/E	SHR	RR	AER	RER
Type of Childhood Cancer§					
Overall	481 / 217.67	2.2 (2.0-2.4)	NA‡	8.4 (7.0-9.8)	NA‡
Leukaemia	104 / 60.78	1.7 (1.4-2.1)	REF	4.7 (2.5-6.9)	REF
Hodgkin's lymphoma	15 / 12.80	1.2 (0.7-1.9)	0.8 (0.4-1.5)	1.1 (-2.6-4.8)	0.8 (0.4-1.6)
NHL	8 / 8.97	0.9 (0.4-1.8)	0.4 (0.1-1.0)	-0.6 (-4.3-3.0)	0.3 (0.1-1.1)
CNS	157 / 50.04	3.1 (2.7-3.7)	1.9 (1.4-2.5)	15.6 (12.0-19.2)	2.0 (1.5-2.6)
Neuroblastoma	34 / 9.47	3.6 (2.6-5.0)	1.1 (0.7-1.9)	17.2 (9.2-25.2)	1.2 (0.7-2.0)
N-Retinoblastoma	5 / 8.33	0.6 (0.2-1.4)	0.5 (0.2-1.1)	-2.9 (-6.8-0.9)	0.4 (0.1-1.2)
H-Retinoblastoma	6 / 5.26	1.1 (0.5-2.5)	0.8 (0.4-1.9)	1.0 (-5.3-7.2)	0.9 (0.4-2.1)
Wilms' tumour	52 / 17.15	3.0 (2.3-4.0)	1.4 (1.0-2.1)	14.2 (8.4-19.9)	1.5 (1.0-2.2)
Bone	23 / 8.90	2.6 (1.7-3.9)	1.9 (1.2-3.2)	12.9 (4.3-21.5)	2.0 (1.2-3.4)
STS	32 / 14.05	2.3 (1.6-3.2)	1.1 (0.7-1.7)	8.8 (3.4-14.2)	1.1 (0.7-1.9)
Other	45 / 21.91	2.1 (1.5-2.8)	1.0 (0.6-1.5)	8.1 (3.5-12.8)	1.0 (0.6-1.5)
P-*Heterogeneity*†			< 0.001		< 0.001
Gender					
Male	139 / 49.04	2.8 (2.4-3.3)	REF	-2.8 (-3.0—2.7)	REF
Female	342 / 168.63	2.0 (1.8-2.3)	0.7 (0.5-0.9)	12.4 (9.8-15.0)	3.3 (2.6-4.1)
P-*Heterogeneity*†			0.002		< 0.001
Attained Age					
5-19	240 / 54.26	4.4 (3.9-5.0)	REF	17.9 (15.0-20.8)	REF
20-29	104 / 79.03	1.3 (1.1-1.6)	0.4 (0.3-0.5)	2.6 (0.5-4.6)	0.6 (0.5-0.8)
30-39	65 / 39.05	1.7 (1.3-2.1)	0.4 (0.3-0.6)	4.2 (1.7-6.8)	0.5 (0.4-0.7)
40-49	48 / 48.96	1.9 (1.4-2.6)	0.4 (0.3-0.6)	6.8 (2.8-10.8)	0.5 (0.4-0.8)
50+	24 / 20.36	1.2 (0.8-1.8)	0.3 (0.2-0.5)	2.1 (-3.5-7.8)	0.7 (0.5-1.0)
P-*Trend*†			< 0.001		< 0.001
Age (Diagnosis)					
0 – 4	245 / 94.68	2.6 (2.3-2.9)	REF	10.2 (8.1-12.2)	REF
5 – 9	118 / 56.93	2.1 (1.7-2.5)	0.9 (0.7-1.2)	7.4 (4.8-10.0)	1.0 (0.7-1.3)
10 – 14	118 / 66.06	1.8 (1.5-2.1)	0.9 (0.7-1.2)	6.3 (3.7-8.9)	1.0 (0.8-1.4)
P-*Trend*†			0.567		0.889
Year (Diagnosis)					
1940 – 1969	69 / 32.68	2.1 (1.7-2.7)	REF	10.1 (5.5-14.6)	REF
1970 – 1979	74 / 38.01	1.9 (1.6-2.4)	1.2 (0.8-1.7)	6.4 (3.4-9.3)	0.7 (0.5-1.1)
1980 – 1989	123 / 59.44	2.1 (1.7-2.5)	1.2 (0.9-1.8)	7.4 (4.8-9.9)	0.8 (0.6-1.1)
1990 – 1999	158 / 68.87	2.3 (2.0-2.7)	0.9 (0.6-1.3)	8.7 (6.3-11.1)	0.7 (0.5-0.9)
2000 – 2006	57 / 18.66	3.1 (2.4-4.0)	0.7 (0.4-1.0)	12.3 (7.6-17.1)	0.3 (0.2-0.5)
P-*Trend*†			0.009		< 0.001

‡Not applicable for overall estimates.

†Not applicable for SHR and AER as these estimates were not calculated using a model.

§Abbreviations: non-Hodgkin's lymphoma (NHL), Central Nervous System (CNS), non-heritable retinoblastoma (N-Retinoblastoma), heritable retinoblastoma (H-Retinoblastoma).

Table 3.5.10 Table of Standardised Hospitalisations Ratios due to other kidney diseases compared to the general population.

	Other Kidney Diseases				
	O/E	SHR	RR	AER	RER
Type of Childhood Cancer§					
Overall	48 / 7.37	6.5 (4.9-8.6)	NA‡	1.3 (0.9-1.8)	NA‡
Leukaemia	6 / 1.73	3.5 (1.6-7.7)	REF	0.5 (-0.1-1.0)	REF
Hodgkin's lymphoma	2 / 0.57	3.5 (0.9-13.9)	1.2 (0.1-11.6)	0.7 (-0.7-2.0)	1.2 (0.1-14.6)
NHL	1 / 0.39	2.6 (0.4-18.4)	1.8 (0.2-16.7)	0.4 (-0.9-1.7)	1.8 (0.2-19.4)
CNS	8 / 1.76	4.6 (2.3-9.1)	1.3 (0.3-5.2)	0.9 (0.1-1.7)	1.3 (0.3-5.9)
Neuroblastoma	6 / 0.30	20.1 (9.0-44.8)	1.5 (0.2-13.6)	3.9 (0.6-7.3)	1.6 (0.2-15.9)
N-Retinoblastoma	2 / 0.30	6.6 (1.6-26.3)	2.3 (0.3-21.8)	15.0 (-9.5-39.5)	2.2 (0.2-28.5)
H-Retinoblastoma	0 / 0.21	0 (NA)	0 (NA)	-0.3 (NA)	0 (NA)
Wilms' tumour	8 / 0.56	14.3 (7.1-28.6)	3.0 (0.7-13.9)	3.0 (0.8-5.2)	3.2 (0.7-15.9)
Bone	2 / 0.32	6.3 (1.6-25.3)	2.3 (0.2-21.7)	1.5 (-1.0-4.0)	2.5 (0.3-24.8)
STS	7 / 0.53	13.3 (6.4-28.0)	6.2 (1.6-23.6)	3.1 (0.6-5.7)	6.8 (1.7-27.4)
Other	6 / 0.71	8.4 (3.8-18.7)	4.0 (1.1-15.4)	1.9 (0.2-3.5)	4.4 (1.1-18.0)
P-*Heterogeneity*†			0.294		0.280
Gender					
Male	22 / 3.98	5.5 (3.6-8.4)	REF	1.1 (0.5-1.6)	REF
Female	26 / 3.39	7.7 (5.2-11.3)	1.2 (0.5-2.6)	1.6 (0.9-2.3)	1.2 (0.5-2.6)
P-*Heterogeneity*†			0.803		0.733
Attained Age					
5-19	25 / 1.39	18.0 (12.2-26.6)	REF	2.3 (1.3-3.2)	REF
20-29	8 / 1.82	4.4 (2.2-8.8)	0.2 (0.1-0.7)	0.6 (0.1-1.2)	0.3 (0.1-0.9)
30-39	9 / 1.64	5.5 (2.9-10.6)	0.2 (0.1-0.7)	1.2 (0.2-2.2)	0.3 (0.1-1.3)
40-49	5 / 1.36	3.7 (1.5-8.8)	0.4 (0.1-1.2)	1.1 (-0.2-2.3)	0.9 (0.3-2.7)
50+	1 / 1.16	0.9 (0.1-6.1)	0.1 (0.0-0.5)	1.0 (-1.2-1.0)	0.4 (0.1-2.2)
P-*Trend*†			0.006		0.382
Age (Diagnosis)					
0 – 4	28 / 3.03	9.2 (6.4-13.4)	REF	1.7 (1.1-2.4)	REF
5 – 9	12 / 1.92	6.2 (3.5-11.0)	1.2 (0.5-3.4)	1.2 (0.4-2.0)	1.2 (0.4-3.4)
10 – 14	8 / 2.42	3..3 (1.7-6.6)	1.2 (0.4-3.8)	0.7 (0.0-1.3)	1.2 (0.4-4.0)
P-*Trend*†			0.659		0.695
Year (Diagnosis)					
1940 – 1969	7 / 1.86	3.8 (1.8-7.9)	REF	1.4 (-0.0-2.8)	REF
1970 – 1979	10 / 1.71	5.9 (3.2-10.9)	1.2 (0.3-4.9)	1.5 (0.4-2.5)	0.7 (0.2-3.2)
1980 – 1989	10 / 1.78	5.6 (3.0-10.4)	1.1 (0.3-4.3)	0.9 (0.2-1.7)	0.5 (0.1-2.0)
1990 – 1999	13 / 1.59	8.2 (4.7-14.0)	2.1 (0.6-7.1)	1.1 (0.4-1.8)	0.8 (0.2-2.7)
2000 – 2006	8 / 0.44	18.4 (9.2-36.7)	1.7 (0.4-6.9)	2.4 (0.6-4.2)	0.5 (0.1-2.2)
P-*Trend*†			0.233		0.535

‡Not applicable for overall estimates.
†Not applicable for SHR and AER as these estimates were not calculated using a model.
§Abbreviations: non-Hodgkin's lymphoma (NHL), Central Nervous System (CNS), non-heritable retinoblastoma (N-Retinoblastoma), heritable retinoblastoma (H-Retinoblastoma).

Table 3.5.11 Table of Standardised Hospitalisations Ratios due to other urinary diseases compared to the general population.

	Other Urinary Diseases				
	O/E	SHR	RR	AER	RER
Type of Childhood Cancer§					
Overall	375 / 335.89	1.1 (1.0-1.2)	NA‡	1.3 (0.0-2.5)	NA‡
Leukaemia	68 / 84.53	0.8 (0.6-1.0)	REF	-1.8 (-3.6-0.0)	REF
Hodgkin's lymphoma	7 / 22..29	0.3 (0.1-0.7)	0.4 (0.2-1.0)	-7.4 (-10.0—4.9)	0.3 (0.1-1.2)
NHL	18 / 14.97	1.2 (0.8-1.9)	1.5 (0.8-2.7)	2.0 (-3.5-7.5)	1.5 (0.8-3.0)
CNS	97 / 79.74	1.2 (1.0-1.5)	1.8 (1.3-2.5)	2.5 (-0.3-5.3)	1.9 (1.3-2.8)
Neuroblastoma	46 / 13.67	3.4 (2.5-4.5)	3.8 (2.5-5.6)	22.8 (13.4-32.2)	4.2 (2.7-6.5)
N-Retinoblastoma	9 / 13.72	0.7 0.3-1.3)	1.0 (0.5-2.2)	-4.2 (-9.4-1.0)	1.0 (0.4-2.5)
H-Retinoblastoma	5 / 9.00	0.6 (0.2-1.3)	0.7 (2.7-2.0)	-5.2 (-10.9-0.5)	0.7 (0.2-2.5)
Wilms' tumour	25 / 26.19	1.0 (0.6-1.4)	1.3 (0.8-2.1)	-0.5 (-4.4-3.5)	1.3 (0.7-2.3)
Bone	14 / 14.60	1.0 (0.6-1.6)	1.5 (0.7-2.9)	-0.5 (-7.3-6.2)	1.6 (0.8-3.3)
STS	53 / 22.55	2.4 (1.8-3.1)	3.4 (2.3-5.0)	15.0 (8.0-22.1)	3.9 (2.5-5.9)
Other	33 / 34.63	1.0 (0.7-1.3)	1.7 (1.1-2.6)	-0.6 (-4.5-3.4)	1.8 (1.1-2.8)
P-*Heterogeneity*†			< 0.001		< 0.001
Gender					
Male	184 / 102.53	1.8 (1.6-2.1)	REF	4.8 (3.3-6.4)	REF
Female	191 / 233.36	0.8 (0.7-0.9)	0.4 (0.3-0.5)	-3.0 (-5.0—1.1)	1.2 (1.0-1.6)
P-*Heterogeneity*†			< 0.001		0.067
Attained Age					
5-19	150 / 65.67	2.3 (1.9-2.7)	REF	8.1 (5.8-10.4)	REF
20-29	87 / 103.06	0.8 (0.7-1.0)	0.4 (0.3-0.6)	-1.6 (-3.5-0.2)	0.6 (0.4-0.8)
30-39	72 / 67.83	1.1 (0.8-1.3)	0.6 (0.4-0.8)	0.7 (-2.0-3.4)	0.9 (0.6-1.3)
40-49	40 / 56.51	0.7 (0.5-1.0)	0.4 (0.3-0.5)	-4.9 (-8.5—1.2)	0.8 (0.5-1.2)
50+	26 / 42.83	0.6 (0.4-0.9)	0.3 (0.2-0.4)	-9.9 (-15.8—4.0)	0.9 (0.6-1.5)
P-*Trend*†			< 0.001		0.636
Age (Diagnosis)					
0 – 4	194 / 138.63	1.4 (1.2-1.6)	REF	3.7 (1.9-5.6)	REF
5 – 9	78 / 87.49	0.9 (0.7-1.1)	0.8 (0.6-1.1)	-1.1 (-3.2-0.9)	0.8 (0.6-1.1)
10 – 14	103 / 109.78	0.9 (0.8-1.1)	0.9 (0.6-1.2)	-0.8 (-3.2-1.6)	0.9 (0.6-1.3)
P-*Trend*†			0.291		0.468
Year (Diagnosis)					
1940 – 1969	78 / 71.84	1.1 (0.9-1.4)	REF	1.7 (-3.1-6.5)	REF
1970 – 1979	67 / 71.56	0.9 (0.7-1.2)	1.1 (0.7-1.5)	-0.8 (-3.6-2.0)	0.6 (0.4-0.9)
1980 – 1989	96 / 85.13	1.1 (0.9-1.4)	1.3 (1.0-1.9)	1.3 (-1.0-3.5)	0.6 (0.4-0.8)
1990 – 1999	93 / 84.64	1.1 (0.9-1.3)	0.9 (0.7-1.3)	8.1 (-1.0-2.6)	0.4 (0.3-0.5)
2000 – 2006	41 / 22.72	1.8 (1.3-2.5)	0.8 (0.5-1.2)	5.9 (1.8-9.9)	0.2 (0.1-0.4)
P-*Trend*†			0.244		< 0.001

‡Not applicable for overall estimates.

†Not applicable for SHR and AER as these estimates were not calculated using a model.

§Abbreviations: non-Hodgkin's lymphoma (NHL), Central Nervous System (CNS), non-heritable retinoblastoma (N-Retinoblastoma), heritable retinoblastoma (H-Retinoblastoma).

4 RISKS OF DIGESTIVE CANCER AMONG 80,483 5-YEAR SURVIVORS OF CHILDHOOD CANCER IN EUROPE: THE PANCARE CHILDHOOD AND ADOLESCENT CANCER SURVIVOR CARE AND FOLLOW-UP STUDIES

Abstract

Background: Five-year survival of childhood cancer has increased substantially over the past few decades. However, the risks of subsequent primary neoplasms (SPN), particularly digestive SPN, remain uncertain in the aging survivor cohort. We investigated risks of developing specific digestive SPNs, particularly by type of childhood cancer in a large-scale cohort.

Methods: The PanCareSurFup (PCSF) cohort includes 80,483 five-year survivors of childhood cancer from 12 countries in Europe. We investigated the risk of developing digestive SPNs by standardised incidence ratios (SIRs) and absolute excess risks (AERs).

Results: Survivors of Wilms' tumour have 15-fold, 9-fold, 56-fold, 11-fold and 24-fold increased risk of digestive cancer overall, colorectal, liver, stomach, and pancreatic cancer, respectively. Survivors of Hodgkin's lymphoma have a 9-fold, 8-fold, 7-fold, 6-fold and 6-fold increased risk of digestive cancer overall, colorectal, liver, stomach and pancreatic cancer, respectively. Survivors of non-Hodgkin's lymphoma have a 6-fold, 7-fold, 6-fold and 6-fold increased risk of colorectal, liver, stomach and pancreatic cancer, respectively. Survivors of neuroblastoma have a 5-fold increased risk of digestive cancer overall and colorectal cancer. Finally, survivors of CNS tumours have 5-fold increased risk of liver cancer.

Conclusion: Survivors of Wilms' tumour experienced the highest excess risk of digestive cancer 15-fold expected, and Wilms' survivors experienced 56-fold, 24-fold, 11-fold and 9-fold excepted risk of liver, pancreatic, stomach and colorectal cancer, respectively. Survivors of Hodgkin's lymphoma experienced the second highest excess risk of digestive cancers 9-fold expected, and Hodgkin's survivors

experienced an 8-fold, 7-fold, 6-fold and 6-fold expected risk of colorectal, liver, stomach and pancreatic cancer, respectively. Such risk stratification information should be very helpful in the development of clinical follow-up guidelines for European survivors.

4.1 Introduction

Over the last few decades five-year survival after childhood cancer has increased substantially to currently over 80%[4]. However, it is widely acknowledged that survivors are at risk of long-term adverse health conditions such as premature mortality and subsequent primary neoplasms (SPN). The risks and causes of SPNs are important to investigate, as it is one of the largest causes of premature mortality in survivors[8,185,186]. Some previous studies have investigated the risk of developing digestive SPNs[38] among survivors of childhood cancer, but most studies lacked statistical power to satisfactorily address the risks of digestive SPNs, particularly beyond age 40 years. The risk of developing any type of digestive SPNs has been previously investigated in smaller scale studies in individual countries[44,74,187-189], but not in a large-scale collaborative study with long follow-up.

We used data from a large-scale Pan-European cohort on over 80,000 survivors of childhood cancer to investigate the risks of digestive SPNs. The main advantage with such a large cohort is that there is substantial amount of follow-up and person-years with over 50% of the cohort having survived at least 25 years. The principal objective of this study was to investigate the risks of developing SPNs in specific sites of the digestive system among 5-year survivors of childhood cancer including; colorectal, liver, stomach, pancreas, small intestine, gallbladder, anus and oesophagus; also to investigate how these risks vary by demographic and cancer related factors such as gender, country, first primary neoplasm (FPN) diagnosis, age at FPN diagnosis, era of FPN diagnosis and attained age.

4.2 Methods

Pan Care Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies (PanCareSurFup)

PanCareSurFup is a consortium of 16 European institutions in 12 countries established in February 2011 and funded by the 7th Framework Programme of the European Commission (www.pancaresurfup.eu)[190]. The global aim of PCSF consortium is to conduct studies into long-term complications of treatment for cancer, to establish guidelines for clinical follow-up of survivors, and to disseminate the results and provide training and workshops for stakeholders. PanCareSurFup is the largest ever collaborative study undertaken to investigate long-term adverse health outcomes among survivors of childhood and adolescent cancer. One of the principal objectives of PanCareSurFup was to estimate risks of developing subsequent primary neoplasms within a large-scale Pan-European cohort of 5-year survivors of a cancer diagnosed under age 20 years. In total, 80,483 survivors of childhood cancer were included ascertained from 12 different cancer registries or major treatment centres across 12 different countries within Europe (Table 4.5.1), including United Kingdom, Norway, Sweden, Finland, Denmark, Iceland, France, Switzerland, Hungary, Slovenia, Italy and the Netherlands. Data relating to each individual cohort was transferred securely to the co-ordinating centre at University of Mainz, Germany, for initial cleaning of data. The individual cohorts were subsequently transferred to the University of Birmingham, UK, for further consistency checks and statistical analyses. Ethical approval for the study was obtained within the country of origin for each contributing cohort separately.

First Primary Neoplasm Ascertainment

First primary neoplasms (FPNs) were classified into groups of childhood cancer type according to the International Classification of Childhood Cancers (ICCC) (3rd revision)[10] by converting all FPN diagnosis codes into the third revision of the International Classification of Diseases for Oncology (ICD-O) using the IARC cancer registry tools software from IARC[191]. Individuals were excluded if their FPN was not convertible to ICD-O or did not have a malignant behaviour code (except for intracranial and bladder tumours for which all behaviour codes were included).

Subsequent Primary Neoplasm Ascertainment

Subsequent primary neoplasms (SPNs) were ascertained using several methods including linkage with population-based cancer registries (Nordic countries, Slovenia, Switzerland and UK), follow-up clinics (Switzerland, France and Hungry), questionnaires (Switzerland, France, Hungary and Netherlands), medical record databases (Hungary, Italy and Netherlands), national mortality records (Switzerland, France and Italy) and health insurance registries (France). For purposes of this study, SPNs were classified by digestive site using the International Classification of Diseases (ICD). The range of codes that identified all digestive SPNs in ICD-10 were C15.0 to C25.9; in ICD-9 were 150.9 to 155.2; in ICD-8 and ICD-7 were 150.0 to 157.9 (Table 4.5.2). Potential SPNs were excluded if the site of development was metastatic or if there was other uncertainty concerning whether it was the primary tumour. All SPNs were validated principally using pathology reports and occasionally other definitive diagnostic reports.

General Population Rates

General population rates were obtained from site-based neoplasm rates relating to as many collaborating countries as possible. The general population neoplasm rates for individual calendar years were downloaded from the European Cancer Observatory (ECO) provided by the International Agency for Research on Cancer (IARC)[192] for Denmark (1978–2007), Finland (1989–2007), Norway (1953–2007), Sweden (1960–2009) and Iceland (1955–2007). Rates for incidence of neoplasms in Slovenia were available for the period 1961–2010 and were downloaded from the Slovenian Epidemiology and Cancer Registry website (SLORA: Slovenia and Cancer)[193]; UK rates were available for the period 1971–2007 from the Office for National Statistics (ONS); and Switzerland rates were available for the period 1985–2010 from the National Institute of Cancer Epidemiology and Registration (NICER). For person-years occurring in calendar years that fell outside of the ranges provided above, rates relating to the nearest calendar year for which rates were available were used as a proxy.

Statistical Analysis

The period at risk of developing a SPN in the digestive system commenced five years from childhood cancer diagnosis and continued until the first occurrence of death, loss to follow-up or study end date. Multiple SPNs per survivor were permitted to avoid bias in comparisons of risks with the general population cancer incidence rates. Standardised incidence ratios (SIR) were calculated as the ratio of observed to expected number of digestive SPNs. Absolute excess risks (AERs) were calculated

from the observed minus expected number of specific digestive SPN, divided by the number of person-years at risk, multiplied by 10,000. Cumulative incidence for specific digestive SPNs was estimated by treating death as a competing risk[155]. Multivariable Poisson regression models were fitted to estimate the relative risk (RR) and the relative excess risk (RER) for SPNs in specific digestive organs taking into account factors attained age, sex, type of childhood cancer, country, age at diagnosis and era of diagnosis. Relative risks (RR) may be interpreted as the ratio of SIRs, adjusted for relevant co-factors fitted. Relative excess risks (RER) may be interpreted as the ratio of AERs, adjusted for relevant co-factors fitted. Statistical significance for all analyses was defined as a 2-sided $P < 0.05$. All analyses were carried out in Stata 13 (StataCorp, College Station, Texas).

4.3 Results

Cohort Characteristics

From the total 80,483 survivors in the cohort, 323 digestive SPNs were observed in 277 survivors. There were 1,276,233 person-years following 5-year survival with mean and median follow-up of 15.6 and 13.8 years, respectively (Table 4.5.3). The majority of SPNs developed in survivors of Hodgkin's disease (N=62), Wilms' tumour (N=53), other tumours (N=50) and tumours of the central nervous system (N=39). From the total number of digestive SPNs, 154 were colorectal, 52 were in the liver, 39 were in the stomach, 33 were in the pancreas, 20 were in the small intestine, 16 were in the oesophagus and 3 were in the anus (Table 4.5.4). In subsequent analysis we only focused on groups with over 20 observed SPNs.

Risk of any digestive subsequent primary neoplasm

Overall, survivors of childhood cancer were nearly 4 times more likely to develop a subsequent cancer in the digestive system compared to expected from the general population (SIR=3.8; 95%CI: 3.4-4.3) with 2 additional cases of subsequent digestive cancer per 10,000 person-years (AER=1.9; 95%CI: 1.6-2.1) (Table 4.5.5). As attained age increased, the number of excess cases of digestive cancers also increased to 8 excess cases observed per 10,000 person-years beyond 50 years of age. Hungary and France exhibited the highest risks of developing a digestive SPN; 20-fold (SIR=20.0; 95%CI; 12.5-32.2) and 10-fold (SIR=10.1; 95%CI: 7.9-12.9) with 3 and 7 excess cases per 10,000 person-years, respectively. Survivors of Wilms' tumour and Hodgkin's' disease were most likely to develop a digestive SPN compared to expected; 15-fold (SIR=14.7; 95%CI: 11.3-19.3) and 9-fold (SIR=8.5;

95%CI: 6.6-10.9), respectively. After adjusting for potential confounding factors, females were 20% less likely to develop a digestive SPN compared to males (RR=0.8; 95%CI: 0.6-1.0). Cumulative incidence of digestive SPN was 1.2% (95%CI: 1.0-1.3) at 50 years of age and 2.2% (95%CI: 1.8-2.6) at 60 years of age; the respective expected cumulative incidence for the general population was 0.4% and 1.4% (Figure 4.5.1).

Risk of subsequent primary colorectal cancer

Survivors experienced 3 times the expected number of colorectal cancers compared to that expected from the general population (SIR=3.2; 95%CI: 2.7-3.7) with 0.8 additional cases of colorectal cancer per 10,000 person-years (AER=0.8; 95%CI: 0.6-1.0) (Table 4.5.6). The absolute excess risk increased significantly with attained age and the highest observed excess risk was 8 excess cases of colorectal SPN per 10,000 person-years among those aged at least 50 years. When evaluating the risks by country, Hungary and France had the highest risks, with 13-fold (SIR=13.1; 95%CI: 6.2-27.4) and 7-fold (SIR=6.5; 95%CI: 4.4-9.7) that expected from the general population, respectively. Survivors of Wilms' tumour and Hodgkin's disease had the highest risk of developing a colorectal SPN, with 9-times (SIR=9.0; 95%CI: 5.8-14.1) and 8-times (SIR=7.9; 95%CI: 5.6-11.2) the risk expected respectively. The excess risk (both RR and RER) of developing a colorectal SPN increased with more recent decade of FPN diagnosis ($p<0.01$) and decreased with increased age at FPN diagnosis ($p<0.01$). At 50 years of age, the cumulative incidence of colorectal cancer for survivors was 0.3% (95%CI: 0.3-0.4) and 1.5% (95%CI: 1.2-1.9) at 60 years of

age; the respective expected cumulative incidence from rates in the general population were 0.2% and 0.8% (Figure 4.5.2).

Risk of subsequent primary liver neoplasm

Survivors were at 10 times (SIR=10.3; 95%CI: 7.9-13.5) the risk of developing primary liver cancer compared to that expected, with 0.4 excess cases of liver cancer per 10,000 person-years (Table 4.5.7). The absolute excess risk increased significantly with increasing attained age and the highest excess risk observed was 4 excess cases of subsequent liver cancer per 10,000 person-years among those aged at least 50 years. Highest risk of developing liver SPNs compared to expected were found in France and Hungary with 45-fold (SIR=45.3; 95%CI: 28.1-72.8) and 38-fold (SIR=37.5; 95%CI: 12.1-116.4) the expected risk, respectively. Survivors of Wilms' tumour, leukaemia and neuroblastoma had the highest risk of developing liver SPNs with 56-fold (SIR=56.0; 95%CI: 33.2-94.6), 15-fold (SIR=15.3; 95%CI: 7.6-30.6) and 15-fold (SIR=15.1; 95%CI: 3.8-60.2) the risk compared to that expected, respectively. After adjusting for other risk factors in multivariable analyses, significant heterogeneity remained by country of residence ($p<0.01$). The cumulative incidence of liver SPN was 0.2% (95%CI: 0.1-0.2) at 50 years of age and 0.4% (95%CI: 0.2-0.5) at 60 years of age, compared to 0.02% and 0.07% from the general population, respectively (Figure 4.5.3).

Risk of subsequent primary stomach neoplasm

Survivors experienced 3 times the number of stomach cancers than expected

(SIR=3.4; 95%CI: 2.5-4.6) with 0.2 excess cases per 10,000 person-years in excess of that expected (Table 4.5.8). Survivors of Wilms' tumour (SIR=11.1; 95%CI: 4.6-26.6) had the highest excess risk, followed by survivors of lymphoma (SIR=6.0; 95%CI: 3.2-11.1). Survivors residing in Hungary (SIR=20.4; 95%CI: 5.1-81.5) and France (SIR=12.3; 95%CI: 6.4-23.7) had the highest risk of developing subsequent stomach cancers compared to the general population. Survivors experienced an excess risk of subsequent stomach cancer with 0.5 excess cases per 10,000 person-years (AER=0.5; 95%CI: 0.2-0.8) at 30-39 years of age. The cumulative incidence of stomach was 0.12% (95%CI: 0.08-0.19) at 50 years of age and 0.27% at 60 years of age, which was twice that of the general population at 50 years of age (0.06%) and increased to 0.17% at 60 years of age (Figure 4.5.4).

Risk of subsequent primary pancreatic neoplasm

Overall, survivors experienced 4-fold the number of pancreatic SPNs (SIR=3.6; 95%CI: 2.5-5.0) with 0.2 excess cases per 10,000 person-years compared to the general population (Table 4.5.9). The risk of developing pancreatic SPNs was greatest for survivors of Wilms' tumour and lymphoma which were 24-fold (SIR=23.8; 95%CI: 11.9-47.7) and 6-fold (SIR=5.5; 95%CI: 2.6-11.4) compared to that expected from the general population, respectively. Survivors residing in Hungary (SIR=35.1; 95%CI: 8.8-140.2) and France (SIR=9.6; 95%CI: 4.3-21.4) experienced the highest risk compared to the general population. Cumulative incidence was 0.1% (95%CI: 0.1-0.2) at 50 years of age and increased to 0.3% (95%CI: 0.2-0.5) at 60 years of age; respective figures for the general population were 0.04% and 0.17% (Figure 4.5.5).

Childhood Cancer Diagnosis

Survivors of Wilms' tumour and Hodgkin's lymphoma appeared to be at the highest risk of developing digestive SPNs; hence we conducted more comprehensive subgroup analyses by specific factors such as sex, age, country of residence, age of FPN diagnosis, decade of FPN diagnosis and attained age. After adjusting for potential confounding factors, the relative risk of developing digestive SPNs for Wilms tumour survivors decreased with increasing attained age compared to the general population ($p=0.033$). However, the absolute excess risk significantly increased with increasing attained age ($p<0.01$) (Table 4.5.10). Cumulative incidence for Wilms' tumour survivors was 5.6% (95%CI: 3.8-7.9) at 50 years of age, which is 14-fold that expected (0.4%) (Figure 4.5.6).

For survivors of Hodgkin's lymphoma, after adjustment for confounders, we found that the absolute excess risk increased substantially with increasing attained age ($p<0.01$). Significant heterogeneity remained between contributing countries (Table 4.5.11). Cumulative incidence for Hodgkin's lymphoma survivors was 3.0% (95%CI: 2.1-4.3) at 50 years of age, which is 7.5-fold that of the expected cumulative incidence (0.4%) (Figure 4.5.7).

4.4 Discussion

To our knowledge, this is the largest ever cohort to investigate the risks of developing SPNs in specific sites of the digestive system among survivors of childhood cancer. The key findings to emerge are summarised in Table 4.5.12. Survivors of Wilms' tumour have 15-fold, 9-fold, 56-fold, 11-fold and 24-fold increased risk of digestive cancer overall, colorectal, liver, stomach, and pancreatic cancer, respectively. Survivors of Hodgkin's lymphoma have a 9-fold, 8-fold, 7-fold, 6-fold and 6-fold increased risk of digestive cancer overall, colorectal, liver, stomach and pancreatic cancer, respectively. Survivors of non-Hodgkin's lymphoma have a 6-fold, 7-fold, 6-fold and 6-fold increased risk of colorectal, liver, stomach and pancreatic cancer, respectively. Survivors of neuroblastoma have a 5-fold increased risk of digestive cancer overall and colorectal cancer. Finally, survivors of CNS tumours have 5-fold increased risk of liver cancer (although there has been discussion regarding the link between CNS tumours and digestive cancers, there has been no large-scale study to show the association between CNS tumours and digestive cancers to date).

Previous studies only had sufficient number of survivors to examine a single site within the digestive system[79,194-199] or the digestive system overall[38,74,187], but we had sufficient numbers of survivors—in our European cohort—to investigate all sites in one study. There was one previous study that also incorporated several countries in Europe which investigated the risk of digestive SPNs but the number of observed SPNs in specific digestive sites was not as high as our cohort[78]. Also, this is the first study to investigate the risks of specific types of digestive SPNs such as liver SPN, stomach SPN and pancreatic SPN by FPN diagnosis.

Our SIR for any digestive SPN was consistent with previous studies with SIRs ranging from 2.1 to 4.8[38,74,187]. Our study also reported similar AERs when taking into account the risk time (person-years); we observed 2 excess cases of digestive SPN in 10,000 survivors per year whereas the previous smaller European study observed 3 excess cases of digestive SPN per 10,000 survivors per year[78].

We anticipated that survivors of Wilms' tumour to be the highest contributor to SPNs in the digestive system in addition to being the highest contributor for colorectal SPNs. However, it has been previously reported that survivors of Hodgkin's lymphoma frequently develop digestive SPNs[195,200-204].

The SIR and excess risk of colorectal SPNs were comparable to previous studies ranging from a relative risk of 7-fold for survivors of Hodgkin's lymphoma to a SIR of 7-fold for overall childhood cancer survivors compared to the general population[78,204] and our cumulative incidence was also similar with 0.2% compared to 0.5% at 40 years of age[195]. Our SIR for colorectal SPN for Hodgkin's lymphoma survivors was substantially lower than CCSS (SIR=36.4; 95%CI: 15.7-71.8)[200], however, only 8 colorectal cancers were observed in the CCSS indicating that their findings may be inaccurate. Almost half of the colorectal SPNs (48%) developed in survivors of Hodgkin's disease (21%), CNS tumours (15%) and Wilms' tumour (12%).

The SIR was significantly elevated for liver, stomach and pancreatic SPNs and is similar to two smaller scale studies[74,78]. However, no previous study has had sufficient statistical power to satisfactorily investigate the risks of liver, stomach and pancreatic SPNs by type of childhood cancer. All categories of childhood cancer, except retinoblastoma, had a significantly higher risk of liver SPNs compared to the general population; survivors of lymphoma, Wilms' tumour, sarcoma and other tumours had a significantly higher risk of stomach SPNs compared to the general population; survivors of lymphoma, Wilms' tumour and other tumours had a significantly higher risk of pancreatic SPNs compared to the general population. Wilms' tumour survivors, of whom a large proportion likely have had their abdominopelvic regions irradiated, are at highest risk of liver (56-fold), stomach (11-fold) and pancreatic (24-fold) SPNs compared to the general population.

Survivors from France had a significantly higher risk compared to survivors residing in other countries. This was most likely due to France, being a hospital-based centre, receiving referrals of complicated cancer cases from different countries and treating them with high dose radiotherapy. However, we cannot rule out that the effect may be due to differences in demographics between countries such as diet, alcohol, smoking, etc.

A guideline from the Children's Oncology Group (COG) recommends that survivors who have received radiotherapy in excess of 30 Gy should receive colonoscopy every 5 years starting at 35 years of age. However, performing colonoscopies in all

survivors of childhood cancer will require a lot of resources and in some cases the benefit of a colonoscopy may not necessarily outweigh the cost (i.e. stress caused by frequently returning to the hospital for tests or only being able to detect a small proportion of secondary digestive malignancies in a large cohort). Therefore, colonoscopies should only be considered for particular survivors who have a significantly high risk.

Study Limitations

Initially, the validation of FPNs in different countries was difficult due to a difference in coding procedures. We managed to convert all the different types of coding, using the IARC registry tool software, into one common class of definitions (ICD-O-3). However, the conversion of codes between different versions of ICD and ICD-O may have resulted in some FPNs being classified as “unknown” or “missing” as cancer classifications are updated over time – but over 90% of codes were successfully converted. Another potential limitation of this study was the lack of information on radiotherapy and chemotherapy exposures given for childhood cancer. Radiotherapy and chemotherapy have been implicated in causing SPNs, but we were not able to stratify the risks of SPN in the digestive system by levels of radiotherapy exposure or chemotherapeutic drug quantities. This study, being multi-national, makes it difficult to infer likely radiotherapy and chemotherapy exposures from FPN and era of FPN diagnosis. Detailed analyses of the risks of SPNs by radiotherapy and chemotherapy exposures would require a nested case-control study, which is currently in progress as part of the PanCareSurFup studies. Another potential limitation relates to the fact that general population cancer incidence rates were not available for France,

Hungary, Italy and the Netherlands. Instead, cancer incidence population rates from the UK were used to estimate the population rates in those countries, which may be under, or overestimating the expected number of digestive SPNs.

Conclusion

Survivors of Wilms' tumour experienced the highest excess risk of digestive cancer 15-fold expected, and Wilms' survivors experienced 56-fold, 24-fold, 11-fold and 9-fold excepted risk of liver, pancreatic, stomach and colorectal cancer, respectively. Survivors of Hodgkin's lymphoma experienced the second highest excess risk of digestive cancers 9-fold expected, and Hodgkin's survivors experienced an 8-fold, 7-fold, 6-fold and 6-fold expected risk of colorectal, liver, stomach and pancreatic cancer, respectively. Such risk stratification information should be very helpful in the development of clinical follow-up guidelines for European survivors – these guidelines may highlight particular groups of survivors who have had abdominal radiation (i.e. Wilms' tumour) for referral to colorectal cancer screening.

4.5 Tables and Figures

Table 4.5.1 Individual cohort characteristics.

Country of origin	Number of 5-year Survivors	Period of Childhood Cancer Diagnosis	Childhood Cancer Ascertainment	Age at Childhood Cancer Diagnosis (in years)	Study Exit (calendar year)	Number of Digestive SPNs	SPN Ascertainment Methods
France	3,138	1946 – 1986	Hospital—based	< 19	2015	64	Various Methods
Hungary	4,885	1971 – 2008	Population—based	< 20	2014	17	Various Methods
Italy (Population)	10,781	1964 – 2005	Population—based	< 20	2014	14	Various Methods
Italy (Hospital)	9,129	1960 – 2008	Hospital—based	< 20	2014	15	Various Methods
Netherlands	6,044	1963 – 2001	Population—based	< 18	2012	17	Various Methods
Denmark	4,832	1943 – 1998	Population—based	< 20	2003	31	Population—based
Sweden	7,709	1958 – 1998	Population—based	< 20	2003	14	Population—based
Norway	3,877	1953 – 1997	Population—based	< 20	2002	12	Population—based
Finland	6,229	1953 – 2006	Population—based	< 20	2012	40	Population—based
Iceland	274	1955 – 1998	Population—based	< 20	2003	0	Population—based
Slovenia	1,252	1960 – 2002	Population—based	< 17	2014	9	Population—based
Switzerland	4,373	1964 – 2005	Population—based	< 20	2014	5	Various Methods
UK	17,960	1940 – 1991	Population—based	< 15	2006	85	Population—based

Table 4.5.2 Table of codes from different versions of the International Classification of Diseases corresponding to specific digestive sites.

ICD-10 Code	ICD-9 Code	ICD-8 Code	ICD-7 Code	Description
C15	150	150	150	Oesophagus
C16	151	151	151	Stomach
C17	152	152	152	Small Intestine
C18	153	153	153	Colon
C19	154.0	154.0	154	Rectosigmoid Junction
C20	154.1	154.1	154	Rectum
C21	154.2 – 154.3	154.2	154*	Anus and Anal Canal
C22	155	155	155.0	Liver and Bile Ducts
C23	156.0	156.0	155.1	Gallbladder
C24	156.1 – 156.9	156.1 – 156.9	155.1	Other Biliary Tract
C25	157	157	157	Pancreas

All codes include the suffix range .0 to .9 in the definitions with exception to codes that already have a specified suffix. *Does not include anus in the definition.

Table 4.5.3 Characteristics of all 80,483 five-year survivors in the European PCSF study and 277 survivors who developed a subsequent cancer in the digestive system.

		All Survivors (N = 80,483)	Survivors who developed Digestive SPN (N = 277)[ɣ]
Sex	Male	43,894 (54.5%)	181 (65.3%)
	Female	36,589 (45.5%)	96 (34.7%)
Age at FPN Diagnosis (years)	Mean	8.1	9.4
	Median	7.0	9.5
	0 – 4	31,892 (39.6%)	79 (28.5%)
	5 – 9	18,565 (23.1%)	65 (23.5%)
	10 – 14	17,712 (22.0%)	77 (27.8%)
	15 – 19	12,314 (15.3%)	56 (20.2%)
Attained Age (years)[‡]	Mean	31.3	37.3
	Median	30.5	36.6
	5 – 9	88 (2.3%)	0 (0.0%)
	10 – 19	681 (18.0%)	22 (7.9%)
	20 – 29	1,057 (27.9%)	62 (22.4%)
	30 – 39	1,078 (28.4%)	86 (31.1%)
	40 – 49	563 (14.8%)	64 (23.1%)
	50 – 59	256 (6.7%)	36 (13.0%)
	60 – 69	66 (1.7%)	7 (2.5%)
	70+	6 (0.2%)	0 (0.0%)
Initial diagnosis	Leukaemia	20,537 (25.5%)	21 (7.6%)
	Hodgkin's Lymphoma	6,595 (8.2%)	54 (19.5%)
	Non-Hodgkin's Lymphoma	3,920 (4.9%)	15 (5.4%)
	CNS	14,469 (18.0%)	37 (13.4%)
	Neuroblastoma	3,971 (4.9%)	8 (2.9%)
	Retinoblastoma	2,500 (3.1%)	5 (1.8%)
	Wilms' Tumour	5,381 (6.7%)	46 (16.6%)
	Bone	3,419 (4.3%)	7 (2.5%)
	Soft Tissue Sarcoma	4,873 (6.1%)	25 (9.0%)
	Other	10,578 (13.1%)	45 (16.3%)
	Unclassified	4,240 (5.3%)	14 (5.1%)
Follow up since 5-year survival from FPT Diagnosis (years)	Mean	15.6	26.3
	Median	13.8	25.7
	0 – 9	28,717 (35.7%)	21 (7.6%)
	10 – 19	25,442 (31.6%)	57 (20.6%)
	20 – 29	16,264 (20.2%)	102 (36.8%)
	30 – 39	7,533 (9.4%)	62 (22.4%)
	40 – 49	2,188 (2.7%)	33 (11.9%)
	50+	339 (0.4%)	2 (0.7%)

[‡]Age at which the survivor first exits the study alive, relating only to development of SPN (N=3,795).
[ɣ]A total of 323 digestive SPNs were observed from 277 survivors.

Table 4.5.4 Frequency of subsequent digestive SPNs stratified by FPN diagnosis for childhood cancer survivors.

First Primary	Total	Colorectal	Liver	Stomach	Pancreas	Small Intestine	Oesophagus	Gallbladder	Anus
Leukaemia	23 (7.1%)	7 (4.5%)	8 (15.4%)	0 (0.0%)	1 (3.0%)	5 (25.0%)	1 (6.3%)	1 (16.7%)	0 (0.0%)
Hodgkin's Lymphoma	62 (19.2%)	32 (20.8%)	4 (7.7%)	10 (25.6%)	6 (18.2%)	1 (5.0%)	6 (37.5%)	2 (33.3%)	1 (33.3%)
NHL	18 (5.6%)	14 (9.1%)	1 (1.9%)	0 (0.0%)	1 (3.0%)	0 (0.0%)	2 (12.5%)	0 (0.0%)	0 (0.0%)
CNS	39 (12.1%)	23 (14.9%)	5 (9.6%)	3 (7.7%)	3 (9.1%)	3 (15.0%)	1 (6.3%)	0 (0.0%)	1 (33.3%)
Neuroblastoma	9 (2.8%)	5 (3.2%)	2 (3.8%)	1 (2.6%)	0 (0.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Retinoblastoma	8 (2.5%)	5 (3.2%)	1 (1.9%)	1 (2.6%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)
Wilms' Tumour	53 (16.4%)	19 (12.3%)	14 (26.9%)	5 (12.8%)	8 (24.2%)	4 (20.0%)	1 (6.3%)	2 (33.3%)	0 (0.0%)
Bone	10 (3.1%)	4 (2.6%)	0 (0.0%)	5 (12.8%)	0 (0.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	0 (0.0%)
STS	32 (9.9%)	14 (9.1%)	5 (9.6%)	3 (7.7%)	4 (12.1%)	3 (15.0%)	1 (6.3%)	1 (16.7%)	1 (16.7%)
Other	50 (15.5%)	21 (13.6%)	9 (17.3%)	7 (17.9%)	9 (27.3%)	2 (10.0%)	2 (12.5%)	0 (0.0%)	0 (0.0%)
Unclassified	19 (5.9%)	10 (6.5%)	3 (5.8%)	4 (10.3%)	1 (3.0%)	1 (5.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Total	323 (100%)	154 (100%)	52 (100%)	39 (100%)	33 (100%)	20 (100%)	16 (100%)	6 (100%)	3 (100%)

Table 4.5.5 Standardised Incidence Ratios and Absolute Excess Risks for subsequent cancer in the digestive system.

Factor	Exposure	O/E	SIR (95% CI)	RR (95% CI)	AER (95% CI)	RER (95% CI)
Overall	All combined	323 / 84.6	3.8 (3.4 – 4.3)	NA[1]	1.9 (1.6 – 2.1)	NA[1]
Sex	Male	202 / 47.9	4.2 (3.7 – 4.8)	1.0 (REF)	2.2 (1.8 – 2.7)	1.0 (REF)
	Female	121 / 36.7	3.3 (2.8 – 3.9)	0.8 (0.6 – 1.0)	1.4 (1.1 – 1.8)	0.6 (0.4 – 0.8)
	Pheterogeneity			0.032		0.001
Cohort	UK	85 / 21.92	3.9 (3.1 – 4.8)	1.0 (REF)	1.7 (1.2 – 2.0)	1.0 (REF)
	France (Villejuif)	64 / 6.35	10.1 (7.9 – 12.9)	2.1 (1.5 – 3.0)	6.9 (5.1 – 8.8)	2.6 (1.7 – 3.9)
	Hungary	17 / 0.85	20.0 (12.5 – 32.2)	2.8 (1.6 – 4.9)	3.2 (1.6 – 4.8)	3.2 (1.7 – 5.9)
	Italy (pop.)	14 / 5.62	2.5 (1.5 – 4.2)	0.6 (0.3 – 1.0)	0.6 (0.1 – 1.2)	0.6 (0.3 – 1.2)
	Italy (hospital)	15 / 1.84	8.1 (4.9 – 13.5)	1.0 (0.6 – 1.8)	1.2 (0.5 – 1.9)	1.0 (0.5 – 1.9)
	Netherlands	17 / 3.54	4.8 (3.0 – 7.7)	0.9 (0.5 – 1.5)	1.3 (0.5 – 2.1)	0.8 (0.4 – 1.7)
	Denmark	31 / 13.48	2.3 (1.6 – 3.3)	1.0 (0.6 – 1.5)	2.2 (0.8 – 3.6)	1.1 (0.6 – 2.1)
	Sweden	14 / 8.03	1.7 (1.0 – 2.9)	0.5 (0.3 – 0.9)	0.5 (0.1 – 1.0)	0.4 (0.2 – 1.0)
	Norway	12 / 4.54	2.6 (1.5 – 4.7)	NA[2]	1.4 (0.1 – 2.6)	NA[2]
	Finland	40 / 14.09	2.8 (2.1 – 3.9)	0.9 (0.6 – 1.4)	2.5 (1.3 – 3.7)	1.1 (0.6 – 2.0)
	Iceland	0 / 0.23	0 (NA)	0 (NA)	-0.7 (NA)	0 (NA)
	Slovenia	9 / 2.79	3.2 (1.7 – 6.2)	NA[2]	2.5 (0.1 – 4.9)	NA[2]
	Switzerland	5 / 1.28	3.9 (1.6 – 9.4)	0.6 (0.2 – 1.6)	0.8 (-0.1 – 1.8)	0.7 (0.2 – 2.5)
	Pheterogeneity			< 0.01		< 0.01
Age at Diagnosis	0-4 yrs	94 / 14.70	6.4 (5.2 – 7.8)	1.0 (REF)	1.5 (1.1 – 1.9)	1.0 (REF)
	5-9 yrs	75 / 14.17	5.3 (4.2 – 6.6)	1.1 (0.8 – 1.5)	2.0 (1.5 – 2.6)	1.2 (0.8 – 1.7)
	10-14 yrs	89 / 28.23	3.2 (2.6 – 3.9)	0.8 (0.6 – 1.2)	2.1 (1.5 – 2.8)	0.8 (0.5 – 1.2)
	15-19yrs	65 / 27.46	2.4 (1.9 – 3.0)	0.9 (0.6 – 1.4)	2.3 (1.3 – 3.3)	0.8 (0.4 – 1.5)
	Ptrend			0.376		0.270
FPN Diagnosis	Leukaemia	23 / 6.17	3.7 (2.5 – 5.6)	1.0 (REF)	0.6 (0.3 – 0.9)	1.0 (REF)
	Hodgkin's Lymphoma	62 / 7.29	8.5 (6.6 – 10.9)	3.7 (2.2 – 6.2)	5.7 (4.1 – 7.3)	4.7 (2.5 – 8.8)
	NHL	18 / 4.56	4.0 (2.5 – 6.3)	1.8 (0.9 – 3.3)	2.2 (0.8 – 3.5)	1.9 (0.8 – 4.3)
	CNS	39 / 17.97	2.2 (1.6 – 3.0)	1.1 (0.6 – 1.9)	0.9 (0.4 – 1.4)	1.1 (0.5 – 2.2)
	Neuroblastoma	9 / 1.76	5.1 (2.7 – 9.8)	1.3 (0.6 – 2.9)	1.1 (0.2 – 2.0)	1.4 (0.5 – 3.5)
	Retinoblastoma	8 / 3.18	2.5 (1.3 – 5.0)	1.1 (0.5 – 2.5)	0.8 (-0.1 – 1.8)	0.7 (0.2 – 2.9)
	Wilms Tumour	53 / 3.60	14.7 (11.3 – 19.3)	3.8 (2.3 – 6.5)	4.8 (3.4 – 6.2)	4.3 (2.3 – 8.3)
	Bone Sarcoma	10 / 6.24	1.6 (0.9 – 3.0)	0.8 (0.4 – 1.8)	0.7 (-0.4 – 1.8)	0.4 (0.1 – 2.8)
	STS	32 / 7.74	4.1 (2.9 – 5.8)	2.0 (1.2 – 3.6)	2.8 (1.5 – 4.1)	2.5 (1.2 – 5.0)
	Other	50 / 19.06	2.6 (2.0 – 3.5)	1.6 (0.9 – 2.7)	1.8 (1.0 – 2.6)	1.7 (0.8 – 3.4)
	Not classifiable	19 / 7.02	2.7 (1.7 – 4.2)	NA[2]	1.8 (0.5 – 3.1)	NA[2]
	Pheterogeneity			< 0.01		< 0.01
Era of Diagnosis	<1970	136 / 57.27	2.4 (2.0 – 2.8)	1.0 (REF)	2.6 (1.8 – 3.3)	1.0 (REF)
	1970-1979	111 / 16.70	6.6 (5.5 – 8.0)	1.5 (1.1 – 2.0)	2.6 (2.0 – 3.2)	1.3 (0.9 – 1.9)
	1980-1989	59 / 8.14	7.2 (5.6 – 9.4)	1.1 (0.7 – 1.7)	1.3 (0.9 – 1.7)	1.1 (0.7 – 1.7)
	1990-1999	14 / 2.23	6.3 (3.7 – 10.6)	0.8 (0.4 – 1.6)	0.6 (0.2 – 1.0)	0.8 (0.4 – 1.8)
	>=2000	3 / 0.22	13.9 (4.5 – 43.2)	1.3 (0.4 – 4.6)	1.1 (-0.2 – 2.3)	1.3 (0.3 – 5.6)
	Ptrend			0.255		0.610
Attained Age	0-19 yrs	25 / 1.69	14.8 (10.0 – 21.8)	1.0 (REF)	0.5 (0.3 – 0.7)	1.0 (REF)
	20-29 yrs	70 / 7.12	9.8 (7.8 – 12.4)	0.6 (0.4 – 1.0)	1.4 (1.1 – 1.8)	2.9 (1.7 – 5.0)
	30-39 yrs	92 / 15.37	6.0 (4.9 – 7.3)	0.4 (0.2 – 0.6)	3.2 (2.4 – 4.0)	7.0 (4.1 – 12.0)
	40-49 yrs	75 / 24.26	3.1 (2.5 – 3.9)	0.2 (0.1 – 0.4)	5.7 (3.8 – 7.5)	14.9 (8.1 – 27.4)
	50+ yrs	61 / 36.11	1.7 (1.3 – 2.2)	0.1 (0.1 – 0.2)	7.8 (3.0 – 12.6)	19.1 (8.2 – 45.0)
	Ptrend			< 0.01		< 0.01

1 Not applicable for overall analysis.
2 Comparison not available due to unsuccessful conversion of ICD-7 codes.

Table 4.5.6 Standardised Incidence Ratios and Absolute Excess Risks for subsequent colorectal cancer.

Factor	Exposure	O/E	SIR (95% CI)	RR (95% CI)	AER (95% CI)	RER (95% CI)
Overall	All combined	154 / 48.46	3.2 (2.7 – 3.7)	NA[1]	0.8 (0.6 – 1.0)	NA[1]
Sex	Male	95 / 25.72	3.7 (3.0 – 4.5)	1.0 (REF)	1.0 (0.7 – 1.3)	1.0 (REF)
	Female	59 / 22.74	2.6 (2.0 – 3.3)	0.8 (0.6 – 1.2)	0.6 (0.4 – 0.9)	0.7 (0.4 – 1.1)
	Pheterogeneity			0.325		0.116
Cohort	UK	52 / 12.55	4.1 (3.2 – 5.4)	1.0 (REF)	2.4 (1.3 – 3.6)	1.0 (REF)
	France Villejuif	24 / 3.68	6.5 (4.4 – 9.7)	1.1 (0.6 – 1.8)	1.3 (0.3 – 2.3)	1.1 (0.6 – 2.1)
	Hungary	7 / 0.54	13.1 (6.2 – 27.4)	1.6 (0.7 – 3.8)	0.4 (-0.0 – 0.6)	1.5 (0.6 – 3.9)
	Italy (pop.)	9 / 3.30	2.7 (1.4 – 5.2)	0.6 (0.3 – 1.3)	0.3 (-0.1 – 0.6)	0.6 (0.2 – 1.6)
	Italy (hospital)	4 / 1.12	3.6 (1.3 – 9.6)	0.5 (0.2 – 1.3)	0.4 (-0.1 – 0.8)	0.4 (0.1 – 1.4)
	Netherlands	6 / 2.14	2.8 (1.3 – 6.2)	0.4 (0.2 – 1.0)	0.6 (-0.3 – 1.5)	0.4 (0.1 – 1.1)
	Denmark	13 / 7.97	1.6 (0.9 – 2.8)	0.7 (0.4 – 1.3)	0.0 (-0.2 – 0.3)	0.7 (0.2 – 2.3)
	Sweden	5 / 4.54	1.1 (0.5 – 2.6)	0.4 (0.2 – 1.1)	0.6 (-0.3 – 1.5)	0.3 (0.0 – 2.8)
	Norway	6 / 2.91	2.1 (0.9 – 4.6)	NA[2]	1.2 (0.4 – 2.0)	NA[2]
	Finland	20 / 7.31	2.7 (1.8 – 4.2)	0.8 (0.4 – 1.4)	-0.4 (NA)	0.6 (0.2 – 1.5)
	Iceland	0 / 0.13	0 (NA)	0 (NA)	1.0 (-0.6 – 2.6)	0 (NA)
	Slovenia	4 / 1.55	2.6 (1.0 – 6.9)	NA[2]	0.7 (-0.1 – 1.6)	NA[2]
	Switzerland	4 / 0.72	5.5 (2.1 – 14.8)	0.9 (0.3 – 2.6)	1.1 (0.7 – 1.5)	1.2 (0.3 – 4.0)
	Pheterogeneity			0.141		< 0.01
Age at Diagnosis	0-4 yrs	41 / 8.56	4.8 (3.5 – 6.5)	1.0 (REF)	0.6 (0.3 – 0.9)	1.0 (REF)
	5-9 yrs	43 / 8.16	5.3 (3.9 – 7.1)	1.0 (0.6 – 1.6)	1.2 (0.7 – 1.6)	0.9 (0.5 – 1.8)
	10-14 yrs	42 / 16.13	2.6 (1.9 – 3.5)	0.4 (0.3 – 0.8)	0.9 (0.5 – 1.4)	0.3 (0.1 – 0.7)
	15-19yrs	28 / 15.61	1.8 (1.2 – 2.6)	0.3 (0.2 – 0.7)	0.8 (0.1 – 1.4)	0.2 (0.0 – 0.5)
	Ptrend			< 0.01		< 0.01
FPN Diagnosis	Leukaemia	7 / 3.70	1.9 (0.9 – 4.0)	1.0 (REF)	0.1 (-0.1 – 0.3)	1.0 (REF)
	Hodgkin's Lymphoma	32 / 4.05	7.9 (5.6 – 11.2)	6.8 (2.9 – 16.0)	2.9 (1.8 – 4.1)	15.5 (3.1 – 67.7)
	NHL	14 / 2.53	5.5 (3.3 – 9.3)	4.5 (1.8 – 11.5)	1.9 (0.7 – 3.0)	9.6 (1.9 – 47.4)
	CNS	23 / 10.17	2.3 (1.5 – 3.4)	2.0 (0.8 – 4.8)	0.5 (0.2 – 1.0)	3.7 (0.8 – 18.0)
	Neuroblastoma	5 / 1.03	4.8 (2.0 – 11.6)	2.7 (0.8 – 8.9)	0.6 (-0.1 – 1.3)	5.3 (0.9 – 32.3)
	Retinoblastoma	5 / 1.81	2.8 (1.1 – 6.6)	1.7 (0.5 – 5.8)	0.5 (-0.2 – 1.3)	2.7 (0.3 – 22.0)
	Wilms Tumour	19 / 2.11	9.0 (5.8 – 14.1)	4.7 (1.9 – 11.6)	1.6 (0.8 – 2.5)	8.7 (1.8 – 42.2)
	Bone Sarcoma	4 / 3.49	1.1 (0.4 – 3.1)	1.2 (0.3 – 4.1)	0.1 (-0.6 – 0.8)	0 (NA)
	STS	14 / 4.36	3.2 (1.9 – 5.4)	2.9 (1.1 – 7.5)	1.1 (0.3 – 2.0)	6.5 (1.3 – 32.5)
	Other	21 / 10.90	1.9 (1.3 – 3.0)	2.3 (0.9 – 5.7)	0.6 (0.1 – 1.1)	2.3 (0.4 – 14.1)
	Not classifiable	10 / 4.29	2.3 (1.3 – 4.3)	NA[2]	0.9 (-0.1 – 1.8)	NA[2]
	Pheterogeneity			< 0.01		< 0.01
Era of Diagnosis	<1970	68 / 32.26	2.1 (1.7 – 2.7)	1.0 (REF)	1.2 (0.6 – 1.7)	1.0 (REF)
	1970-1979	52 / 9.64	5.4 (4.1 – 7.1)	3.2 (1.9 – 5.2)	1.2 (0.8 – 1.6)	5.3 (2.3 – 12.0)
	1980-1989	24 / 4.94	4.9 (3.3 – 7.2)	3.1 (1.5 – 6.2)	0.5 (0.2 – 0.7)	7.0 (2.4 – 20.6)
	1990-1999	7 / 1.46	4.8 (2.3 – 10.0)	4.1 (1.4 – 11.9)	0.3 (0.0 – 0.6)	14.0 (3.1 – 64.6)
	>=2000	3 / 0.15	19.6 (6.3 – 60.7)	16.4 (3.8 – 70.5)	1.1 (-0.2 – 2.4)	84.1 (12.5 – 564.0)
	Ptrend			< 0.01		< 0.01
Attained Age	0-19 yrs	4 / 0.98	4.1 (1.5 – 10.8)	1.0 (REF)	0.1 (-0.0 – 0.2)	1.0 (REF)
	20-29 yrs	27 / 4.47	6.0 (4.1 – 8.8)	1.6 (0.5 – 4.5)	0.5 (0.3 – 0.7)	7.6 (2.1 – 27.2)
	30-39 yrs	37 / 8.95	4.1 (3.0 – 5.7)	1.1 (0.4 – 3.2)	1.2 (0.7 – 1.7)	19.4 (5.4 – 69.3)
	40-49 yrs	39 / 13.65	2.9 (2.1 – 3.9)	0.9 (0.3 – 2.5)	2.8 (1.5 – 4.2)	64.7 (18.0 – 232.7)
	50+ yrs	47 / 20.41	2.3 (1.7 – 3.1)	0.8 (0.3 – 2.4)	8.3 (4.1 – 12.5)	164.5 (42.4 – 638.8)
	Ptrend			0.065		< 0.01

1 Not applicable for overall analysis.
2 Comparison not available due to unsuccessful conversion of ICD-7 codes.

Table 4.5.7 Standardised Incidence Ratios and Absolute Excess Risks for subsequent liver cancer.

Factor	Exposure[α]	O/E	SIR (95% CI)	RR (95% CI)	AER (95% CI)	RER (95% CI)
Overall	All combined	52 / 5.04	10.3 (7.9 – 13.5)	NA[1]	0.4 (0.3 – 0.5)	NA[1]
Sex	Male	33 / 3.26	10.1 (7.2 – 14.2)	1.0 (REF)	0.4 (0.3 – 0.6)	1.0 (REF)
	Female	19 / 1.78	10.7 (6.8 – 16.7)	0.8 (0.4 – 1.5)	0.3 (0.2 – 0.4)	0.4 (0.3 – 1.0)
	Pheterogeneity			0.447		0.017
Cohort	UK	7 / 1.28	5.5 (2.6 – 11.5)	1.0 (REF)	0.2 (0.0 – 0.3)	1.0 (REF)
	France Villejuif	17 / 0.38	45.3 (28.1 – 72.8)	6.1 (2.4 – 15.7)	2.0 (1.0 – 3.0)	7.5 (2.4 – 20.2)
	Hungary	3 / 0.08	37.5 (12.1 – 116.4)	6.4 (1.5 – 26.4)	0.6 (-0.1 – 1.3)	8.0 (1.7 – 35.6)
	Italy [α]	8 / 0.58	13.9 (6.9 – 27.8)	2.2 (0.8 – 6.3)	0.3 (0.1 – 0.5)	2.5 (0.7 – 8.2)
	Netherlands	1 / 0.26	3.9 (0.5 – 27.7)	0.6 (0.1 – 5.0)	0.1 (-0.1 – 0.3)	0.1 (NA)
	Nordic countries[α]	14 / 2.22	6.3 (3.7 – 10.7)	1.8 (0.6 – 4.9)	0.3 (0.1 – 0.5)	2.0 (0.6 – 7.3)
	Slovenia	2 / 0.13	15.0 (3.8 – 60.0)	NA[2]	0.8 (-0.4 – 1.9)	NA[2]
	Switzerland	0 / 0.13	0 (NA)	0.0 (NA)	-0.0 (NA)	0.0 (NA)
	Pheterogeneity			< 0.01		< 0.01
Age at Diagnosis	0-4 yrs	24 / 1.11	21.6 (14.5 – 32.2)	1.0 (REF)	0.4 (0.3 – 0.6)	1.0 (REF)
	5-9 yrs	11 / 0.93	11.8 (6.5 – 21.2)	0.9 (0.4 – 1.9)	0.3 (0.1 – 0.6)	1.0 (0.4 – 2.2)
	10-14 yrs	12 / 1.56	7.7 (4.4 – 13.5)	0.7 (0.3 – 1.7)	0.4 (0.1 – 0.6)	0.7 (0.2 – 2.0)
	15-19yrs	5 / 1.44	3.5 (1.4 – 8.4)	0.4 (0.1 – 1.4)	0.2 (-0.1 – 0.5)	0.3 (0.0 – 2.0)
	Ptrend			0.037		0.183
FPN Diagnosis	Leukaemia	8 / 0.52	15.3 (7.6 – 30.6)	1.0 (REF)	0.3 (0.1 – 0.5)	1.0 (REF)
	Lymphoma[α]	5 / 0.73	6.8 (2.8 – 16.4)	0.5 (0.2 – 1.8)	0.3 (-0.0 – 0.6)	0.5 (0.1 – 2.2)
	CNS	5 / 1.06	4.7 (2.0 – 11.3)	0.4 (0.1 – 1.3)	0.2 (-0.0 – 0.4)	0.2 (0.0 – 2.0)
	Neuroblastoma	2 / 0.13	15.1 (3.8 – 60.2)	0.6 (0.1 – 3.0)	0.3 (-0.1 – 0.7)	0.4 (0.1 – 3.3)
	Retinoblastoma	1 / 0.19	5.2 (0.7 – 36.7)	0.3 (0.0 – 3.0)	0.1 (-0.2 – 0.5)	0.2 (0.0 – 5.9)
	Wilms Tumour	14 / 0.25	56.0 (33.2 – 94.6)	2.0 (0.7 – 5.7)	1.3 (0.6 – 2.0)	1.9 (0.6 – 5.9)
	Sarcoma[α]	5 / 0.81	6.1 (2.6 – 14.8)	0.3 (0.1 – 1.3)	0.3 (-0.0 – 0.6)	0.3 (0.1 – 1.6)
	Other	9 / 1.04	8.6 (4.5 – 16.6)	0.8 (0.3 – 2.4)	0.5 (0.1 – 0.8)	0.9 (0.2 – 3.1)
	Not classifiable	3 / 0.30	10.1 (3.3 – 31.3)	NA[2]	0.4 (-0.1 – 0.9)	NA[2]
	Pheterogeneity			0.037		0.017
Era of Diagnosis	<1970	22 / 2.95	7.5 (4.9 – 11.3)	1.0 (REF)	0.6 (0.3 – 0.9)	1.0 (REF)
	1970-1979	20 / 1.10	18.1 (11.7 – 28.1)	1.7 (0.8 – 3.8)	0.5 (0.3 – 0.8)	1.8 (0.8 – 4.7)
	≥1980[α]	10 / 0.99	10.1 (5.5 – 18.9)	0.8 (0.3 – 2.4)	0.1 (0.1 – 0.3)	0.7 (0.2 – 2.7)
	Ptrend			0.647		0.639
Attained Age	0-29 yrs[α]	17 / 1.15	14.7 (9.2 – 23.7)	1.0 (REF)	0.2 (0.1 – 0.3)	1.0 (REF)
	30-39 yrs	12 / 0.84	14.3 (8.1 – 25.3)	1.1 (0.5 – 2.5)	0.5 (0.2 – 0.8)	3.6 (1.5 – 8.6)
	40-49 yrs	10 / 1.19	8.4 (4.5 – 15.6)	0.8 (0.3 – 1.8)	1.0 (0.3 – 1.7)	9.7 (3.9 – 24.6)
	50+ yrs	13 / 1.86	7.0 (4.1 – 12.0)	0.8 (0.4 – 2.0)	3.5 (1.3 – 5.7)	32.6 (10.8 – 98.2)
	Ptrend			0.635		< 0.01

[α] Some exposures were grouped together for this analysis due to very small numbers.
1 Not applicable for overall analysis.
2 Comparison not available due to unsuccessful conversion of ICD-7 codes.

Table 4.5.8 Standardised Incidence Ratios and Absolute Excess Risks for subsequent stomach cancer.

Factor	Exposure[α]	O/E	SIR (95% CI)	RR (95% CI)	AER (95% CI)	RER (95% CI)
Overall	All combined	39 / 11.57	3.4 (2.5 – 4.6)	NA[1]	0.2 (0.1 – 0.3)	NA[1]
Sex	Male	22 / 7.04	3.1 (2.1 – 4.7)	NA[2]	0.2 (0.1 – 0.4)	NA[2]
	Female	17 / 4.53	3.8 (2.3 – 6.0)	NA[2]	0.2 (0.1 – 0.4)	NA[2]
	Pheterogeneity					
Cohort	UK	8 / 2.83	2.8 (1.4 – 5.7)	NA[2]	0.1 (-0.0 – 0.3)	NA[2]
	France (Villejuif)	9 / 0.73	12.3 (6.4 – 23.7)	NA[2]	1.0 (0.3 – 1.7)	NA[2]
	Hungary	2 / 0.10	20.4 (5.1 – 81.5)	NA[2]	0.4 (-0.2 – 0.9)	NA[2]
	Italy [α]	3 / 0.91	3.3 (1.1 – 10.2)	NA[2]	0.3 (0.1 – 0.5)	NA[2]
	Netherlands	3 / 0.41	7.3 (2.4 – 22.7)	NA[2]	0.3 (-0.1 – 0.6)	NA[2]
	Nordic countries[α]	13 / 5.81	2.2 (1.3 – 3.9)	NA[2]	0.3 (0.1 – 0.5)	NA[2]
	Slovenia	1 / 0.56	1.8 (0.3 – 12.7)	NA[2]	0.2 (-0.6 – 1.0)	NA[2]
	Switzerland	0 / 0.23	0.0 (NA)	NA[2]	-0.0 (NA)	NA[2]
	Pheterogeneity					
Age at Diagnosis	0-9 yrs[α]	10 / 3.80	2.6 (1.4 – 4.9)	NA[2]	0.1 (0.0 – 0.2)	NA[2]
	10-14 yrs	16 / 3.80	4.2 (2.6 – 6.9)	NA[2]	0.4 (0.2 – 0.7)	NA[2]
	15-19yrs	13 / 3.97	3.3 (1.9 – 5.6)	NA[2]	0.6 (0.1 – 1.0)	NA[2]
	Ptrend					
FPN Diagnosis	Leukaemia	0 / 0.79	0.0 (NA)	NA[2]	-0.0 (NA)	NA[2]
	Lymphoma[α]	10 / 1.67	6.0 (3.2 – 11.1)	NA[2]	0.5 (0.1 – 0.9)	NA[2]
	CNS	3 / 2.44	1.2 (0.4 – 3.8)	NA[2]	0.0 (-0.1 – 0.2)	NA[2]
	Neuroblastoma	1 / 0.22	4.5 (0.6 – 32.1)	NA[2]	0.1 (-0.2 – 0.4)	NA[2]
	Retinoblastoma	1 / 0.42	2.4 (0.3 – 17.0)	NA[2]	0.1 (-0.2 – 0.4)	NA[2]
	Wilms Tumour	5 / 0.45	11.1 (4.6 – 26.6)	NA[2]	0.4 (0.0 – 0.9)	NA[2]
	Sarcoma[α]	8 / 1.88	4.3 (2.1 – 8.5)	NA[2]	0.4 (0.0 – 0.8)	NA[2]
	Other	7 / 2.58	2.7 (1.3 – 5.7)	NA[2]	0.3 (-0.0 – 0.6)	NA[2]
	Not classifiable	4 / 1.11	3.6 (1.4 – 9.6)	NA[2]	0.4 (-0.2 – 1.0)	NA[2]
	Pheterogeneity					
Era of Diagnosis	<1970	13 / 7.71	1.7 (1.0 – 2.9)	NA[2]	0.2 (-0.1 – 0.4)	NA[2]
	1970-1979	13 / 2.43	5.3 (3.1 – 9.2)	NA[2]	0.3 (0.1 – 0.5)	NA[2]
	≥1980[α]	13 / 1.43	9.1 (5.3 – 15.7)	NA[2]	0.2 (0.1 – 0.3)	NA[2]
	Ptrend					
Attained Age	0-29 yrs[α]	6 / 1.17	5.1 (2.3 – 11.4)	NA[2]	0.1 (0.0 – 0.1)	NA[2]
	30-39 yrs	14 / 2.67	5.3 (3.1 – 8.9)	NA[2]	0.5 (0.2 – 0.8)	NA[2]
	40-49 yrs	9 / 3.63	2.5 (1.3 – 4.8)	NA[2]	0.6 (-0.1 – 1.3)	NA[2]
	50+ yrs	10 / 4.11	2.4 (1.3 – 4.5)	NA[2]	1.8 (-0.1 – 3.8)	NA[2]
	Ptrend					

[α] Some exposures were grouped together for this analysis due to very small numbers.
1 Not applicable for overall analysis.
2 Comparison not available due to low numbers.

Table 4.5.9 Standardised Incidence Ratios and Absolute Excess Risks for subsequent pancreatic cancer.

Factor	Exposure[α]	O/E	SIR (95% CI)	RR (95% CI)	AER (95% CI)	RER (95% CI)
Overall	All combined	33 / 9.23	3.6 (2.5 – 5.0)	NA[1]	0.2 (0.1 – 0.3)	NA[1]
Sex	Male	21 / 5.12	4.1 (2.7 – 6.3)	NA[2]	0.2 (0.1 – 0.4)	NA[2]
	Female	12 / 4.11	2.9 (1.7 – 5.1)	NA[2]	0.1 (0.0 – 0.3)	NA[2]
	Pheterogeneity					
Cohort	UK	8 / 2.14	3.7 (1.9 – 7.5)	NA[2]	0.2 (0.0 – 0.3)	NA[2]
	France (Villejuif)	6 / 0.62	9.6 (4.3 – 21.4)	NA[2]	0.6 (0.1 – 1.2)	NA[2]
	Hungary	2 / 0.06	35.1 (8.8 – 140.2)	NA[2]	0.4 (-0.1 – 0.9)	NA[2]
	Italy[α]	3 / 0.91	3.3 (1.1 – 10.2)	NA[2]	0.1 (-0.1 – 0.2)	NA[2]
	Netherlands	2 / 0.29	6.8 (1.7 – 27.2)	NA[2]	0.2 (-0.1 – 0.4)	NA[2]
	Nordic countries[α]	11 / 5.81	1.9 (1.0 – 3.4)	NA[2]	0.1 (-0.0 – 0.3)	NA[2]
	Slovenia	1 / 0.28	3.6 (0.5 – 25.5)	NA[2]	0.3 (-0.5 – 1.1)	NA[2]
	Switzerland	0 / 0.10	0.0 (NA)	NA[2]	-0.0 (NA)	NA[2]
	Pheterogeneity					
Age at Diagnosis	0-4 yrs	8 / 1.37	5.9 (2.9 – 11.7)	NA[2]	0.1 (0.0 – 0.2)	NA[2]
	5-9 yrs	9 / 1.40	6.4 (3.4 – 12.4)	NA[2]	0.3 (0.1 – 0.5)	NA[2]
	10-14 yrs	8 / 3.05	2.6 (1.3 – 5.2)	NA[2]	0.2 (-0.0 – 0.4)	NA[2]
	15-19yrs	8 / 3.42	2.3 (1.2 – 4.7)	NA[2]	0.3 (-0.1 – 0.6)	NA[2]
	Ptrend					
FPN Diagnosis	Leukaemia	1 / 0.50	2.0 (0.3 – 14.2)	NA[2]	0.0 (-0.1 – 0.1)	NA[2]
	Lymphoma[α]	7 / 1.28	5.5 (2.6 – 11.4)	NA[2]	0.4 (0.0 – 0.7)	NA[2]
	CNS	3 / 2.01	1.5 (0.5 – 4.6)	NA[2]	0.0 (-0.1 – 0.2)	NA[2]
	Neuroblastoma	0 / 0.16	0.0 (NA)	NA[2]	-0.0 (NA)	NA[2]
	Retinoblastoma	0 / 0.33	0.0 (NA)	NA[2]	-0.1 (NA)	NA[2]
	Wilms Tumour	8 / 0.34	23.8 (11.9 – 47.7)	NA[2]	0.7 (0.2 – 1.3)	NA[2]
	Sarcoma[α]	4 / 1.62	2.5 (0.9 – 6.6)	NA[2]	0.2 (-0.1 – 0.5)	NA[2]
	Other	9 / 2.32	3.9 (2.0 – 7.5)	NA[2]	0.4 (0.1 – 0.7)	NA[2]
	Not classifiable	1 / 0.67	1.5 (0.2 – 10.5)	NA[2]	0.1 (-0.3 – 0.4)	NA[2]
	Pheterogeneity					
Era of Diagnosis	<1970	16 / 6.96	2.3 (1.4 – 3.8)	NA[2]	0.3 (0.0 – 0.6)	NA[2]
	1970-1979	13 / 1.55	8.4 (4.9 – 14.5)	NA[2]	0.3 (0.1 – 0.5)	NA[2]
	≥1980[α]	4 / 0.73	5.5 (2.1 – 14.6)	NA[2]	0.1 (-0.0 – 0.1)	NA[2]
	Ptrend					
Attained Age	0-29 yrs[α]	5 / 0.46	10.9 (4.5 – 26.2)	NA[2]	0.0 (0.0 – 0.1)	NA[2]
	30-39 yrs	9 / 1.35	6.7 (3.5 – 12.8)	NA[2]	0.3 (0.1 – 0.6)	NA[2]
	40-49 yrs	9 / 2.58	3.5 (1.8 – 6.7)	NA[2]	0.7 (0.1 – 1.4)	NA[2]
	50+ yrs	10 / 4.84	2.1 (1.1 – 3.8)	NA[2]	1.6 (-0.3 – 3.6)	NA[2]
	Ptrend					

[α] Some exposures were grouped together for this analysis due to very small numbers.
1 Not applicable for overall analysis.
2 Comparison not available due to low numbers.

Table 4.5.10 Standardised Incidence Ratios and Absolute Excess Risks of subsequent digestive cancer in Wilms' tumour survivors.

Factor	Exposure	O/E	SIR (95% CI)	RR (95% CI)	AER (95% CI)	RER (95% CI)
Overall	All combined	53 / 3.60	14.7 (11.3 – 19.3)	NA[1]	4.8 (3.4 – 6.2)	NA[1]
Sex	Male	33 / 1.98	16.7 (11.8 – 23.4)	1.0 (REF)	6.0 (3.8 – 8.1)	1.0 (REF)
	Female	20 / 1.62	12.4 (8.0 – 19.2)	0.7 (0.4 – 1.3)	3.6 (1.9 – 5.3)	0.6 (0.3 – 1.1)
	Pheterogeneity			0.245		0.073
Cohort	UK	13 / 1.26	10.3 (6.0 – 17.8)	1.0 (REF)	3.4 (1.4 – 5.5)	1.0 (REF)
	France	24 / 1.16	20.6 (13.8 – 30.7)	2.2 (1.1 – 4.4)	12.1 (7.0 – 17.2)	2.6 (1.2 – 5.3)
	Hungary	2 / 0.04	51.4 (12.9 – 205.6)	4.3 (0.9 – 20.60)	5.2 (-2.2 – 12.5)	4.5 (0.9 – 22.9)
	Italy	3 / 0.26	11.5 (3.7 – 35.6)	1.0 (0.3 – 3.5)	1.8 (-0.4 – 4.0)	0.9 (0.2 – 3.6)
	Netherlands	4 / 0.25	16.1 (6.1 – 42.9)	1.4 (0.4 – 4.5)	3.2 (-0.2 – 6.6)	1.5 (0.4 – 5.0)
	Nordic countries	7 / 0.59	11.9 (5.7 – 24.9)	1.2 (0.5 – 3.0)	4.0 (0.8 – 7.3)	1.3 (0.5 – 3.6)
	Slovenia	0 / 0.01	0.0 (NA)	NA[2]	-0.1 (NA)	NA[2]
	Switzerland	0 / 0.03	0.0 (NA)	0.0 (NA)	-0.1 (NA)	0.0 (NA)
	Pheterogeneity			0.257		0.183
Age at Diagnosis	0-4 yrs	37 / 2.67	13.9 (10.1 – 19.2)	1.0 (REF)	4.2 (2.7 – 5.6)	1.0 (REF)
	5-9 yrs	11 / 0.74	14.8 (8.2 – 26.7)	1.1 (0.6 – 2.2)	5.5 (2.0 – 9.0)	1.2 (0.6 – 2.5)
	10-19 yrs	5 / 0.19	26.6 (11.1 – 64.0)	2.7 (1.0 – 7.0)	20.2 (1.8 – 38.6)	3.5 (1.3 – 9.5)
	Ptrend			0.134		0.079
Era of Diagnosis	<1970	27 / 2.37	11.4 (7.8 – 16.60	1.0 (REF)	9.2 (5.4 – 13.1)	1.0 (REF)
	1970-1979	22 / 0.84	26.2 (17.3 – 37.8)	1.4 (0.7 – 2.7)	6.1 (3.5 – 8.7)	1.1 (0.6 – 2.2)
	1980-2009	4 / 0.39	10.2 (3.8 – 27.2)	0.4 (0.1 – 1.4)	0.9 (-0.1 – 1.8)	0.3 (0.1 – 1.2)
	Ptrend			0.959		0.533
Attained Age	0-29 yrs	13 / 0.63	20.5 (11.9 – 35.4)	1.0 (REF)	1.5 (0.6 – 2.3)	1.0 (REF)
	30-39 yrs	19 / 0.94	20.3 (13.0 – 31.8)	0.7 (0.3 – 1.4)	12.2 (6.4 – 18.0)	5.3 (2.5 – 11.50
	40+ yrs	21 / 2.03	10.4 (6.7 – 15.9)	0.3 (0.1 – 0.8)	33.9 (17.9 – 50.0)	13.0 (5.5 – 30.6)
	Ptrend			0.033		< 0.01

1 Not applicable for overall analysis.
2 Comparison not available due to unsuccessful conversion of ICD-7 codes.

Table 4.5.11 Standardised Incidence Ratios and Absolute Excess Risks of subsequent digestive cancer in Hodgkin's lymphoma survivors.

Factor	Exposure	O/E	SIR (95% CI)	RR (95% CI)	AER (95% CI)	RER (95% CI)
Overall	All combined	62 / 7.29	8.5 (6.6 – 10.9)	NA[1]	5.7 (4.1 – 7.3)	NA[1]
Sex	Male	44 / 4.98	8.8 (6.6 – 11.9)	1.0 (REF)	6.3 (4.2 – 8.4)	1.0 (REF)
	Female	18 / 2.31	7.8 (4.9 – 12.4)	0.9 (0.5 – 1.5)	4.6 (2.1 – 7.0)	0.7 (0.4 – 1.3)
	Pheterogeneity			0.570		0.272
Cohort	UK	13 / 2.30	5.6 (3.3 – 9.7)	1.0 (REF)	3.9 (1.3 – 6.5)	1.0 (REF)
	France	11 / 0.47	23.2 (12.8 – 41.9)	4.1 (1.8 – 9.3)	19.6 (7.5 – 31.7)	4.8 (1.9 – 11.9)
	Hungary	4 / 0.12	34.6 (13.0 – 92.1)	5.8 (1.7 – 19.4)	8.6 (-0.1 – 17.2)	6.9 (1.9 – 25.2)
	Italy	8 / 0.98	8.2 (4.1 – 16.3)	1.4 (0.6 – 3.4)	3.0 (0.6 – 5.4)	1.4 (0.5 – 3.9)
	Netherlands	4 / 0.31	12.8 (4.8 – 34.0)	2.2 (0.7 – 7.3)	5.4 (-0.3 – 11.1)	2.5 (0.7 – 9.8)
	Nordic countries	21 / 2.87	7.3 (4.8 – 11.2)	1.6 (0.8 – 3.2)	7.8 (3.9 – 11.7)	1.9 (0.8 – 4.2)
	Slovenia	0 / 0.06	0.0 (NA)	NA[2]	-0.4 (NA)	NA[2]
	Switzerland	1 / 0.17	5.8 (0.8 – 41.4)	1.1 (0.1 – 8.8)	2.1 (-2.9 – 7.1)	1.4 (0.2 – 12.9)
	Pheterogeneity			0.026		0.023
Age at Diagnosis	0-4 yrs	2 / 0.20	9.8 (2.4 – 39.1)	1.0 (REF)	2.6 (-1.4 – 6.5)	1.0 (REF)
	5-9 yrs	17 / 1.15	14.8 (9.2 – 23.8)	1.6 (0.4 – 7.0)	6.6 (3.3 – 10.0)	1.9 (0.4 – 9.9)
	10-19 yrs	43 / 5.93	7.2 (5.4 – 9.8)	1.1 (0.3 – 4.5)	5.7 (3.7 – 7.7)	1.5 (0.3 – 7.4)
	Ptrend			0.418		0.847
Era of Diagnosis	<1970	26 / 3.99	6.5 (4.4 – 9.6)	1.0 (REF)	12.3 (6.7 – 17.9)	1.0 (REF)
	1970-1979	25 / 1.97	12.7 (8.6 – 18.8)	1.2 (0.6 – 2.2)	7.9 (4.5 – 11.2)	0.8 (0.4 – 1.6)
	1980-2009	11 / 1.33	8.3 (4.6 – 14.9)	0.5 (0.2 – 1.3)	2.0 (0.7 – 3.3)	0.3 (0.1 – 0.9)
	Ptrend			0.654		0.096
Attained Age	0-29 yrs	9 / 0.77	11.7 (6.1 – 22.5)	1.0 (REF)	1.4 (0.4 – 2.3)	1.0 (REF)
	30-39 yrs	23 / 1.59	14.5 (9.6 – 21.8)	1.1 (0.5 – 2.4)	8.7 (4.9 – 12.5)	5.8 (2.4 – 13.6)
	40+ yrs	30 / 4.93	6.1 (4.3 – 8.7)	0.4 (0.2 – 1.0)	13.3 (33.2)	11.8 (4.7 – 29.4)
	Ptrend			0.094		< 0.01

1 Not applicable for overall analysis.
2 Comparison not available due to unsuccessful conversion of ICD-7 codes.

Table 4.5.12 SIRs and 95% confidence intervals for FPNs of at least 5-fold expected and based on at least 5 observed SPN cancers of specified site.

FPN	Digestive	Colorectal	Liver	Stomach	Pancreatic
Leukaemia	-	-	15.3 (7.6 – 30.6)	-	-
Hodgkin's lymphoma	8.5 (6.6 – 10.9)	7.9 (5.6 – 11.2)	6.8 (2.8 – 16.4)[1]	6.0 (3.2 – 11.1)[1]	5.5 (2.6 – 11.4)[1]
NHL	-	5.5 (3.3 – 9.3)			
CNS	-	-	4.7 (2.0 – 11.3)	-	-
Neuroblastoma	5.1 (2.7 – 9.8)	4.8 (2.0 – 11.6)	-	-	-
Retinoblastoma	-	-	-	-	-
Wilms' tumour	14.7 (11.3 – 19.3)	9.0 (5.8 – 14.1)	56.0 (33.2 – 94.6)	11.1 (4.6 – 26.6)	23.8 (11.9 – 47.7)
Bone	-	-	6.1 (2.6 – 14.8)[2]	-	-
STS	-	-			
Other	-	-	8.6 (4.5 – 16.6)	-	-

1 Hodgkin's lymphoma and NHL combined due to insufficient numbers.
2 Bone sarcoma and STS combined due to insufficient numbers.

Figure 4.5.1 Cumulative incidence of developing a digestive SPN among survivors of childhood cancer with 95% confidence intervals and the corresponding cumulative incidence expected from the general population.

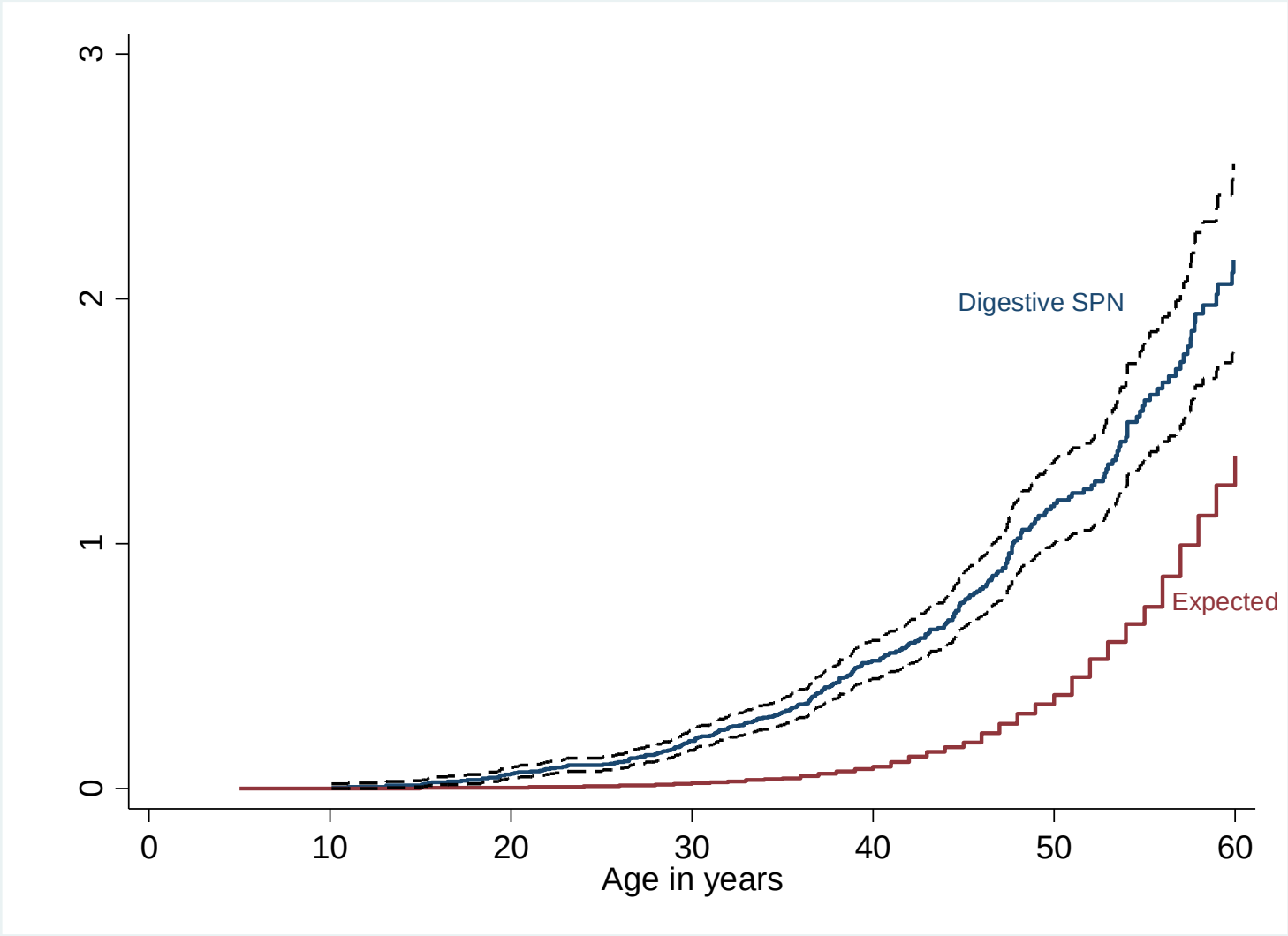


Figure 4.5.2 Cumulative incidence of developing a colorectal cancer among survivors with 95% confidence intervals and the corresponding cumulative incidence expected from the general population.

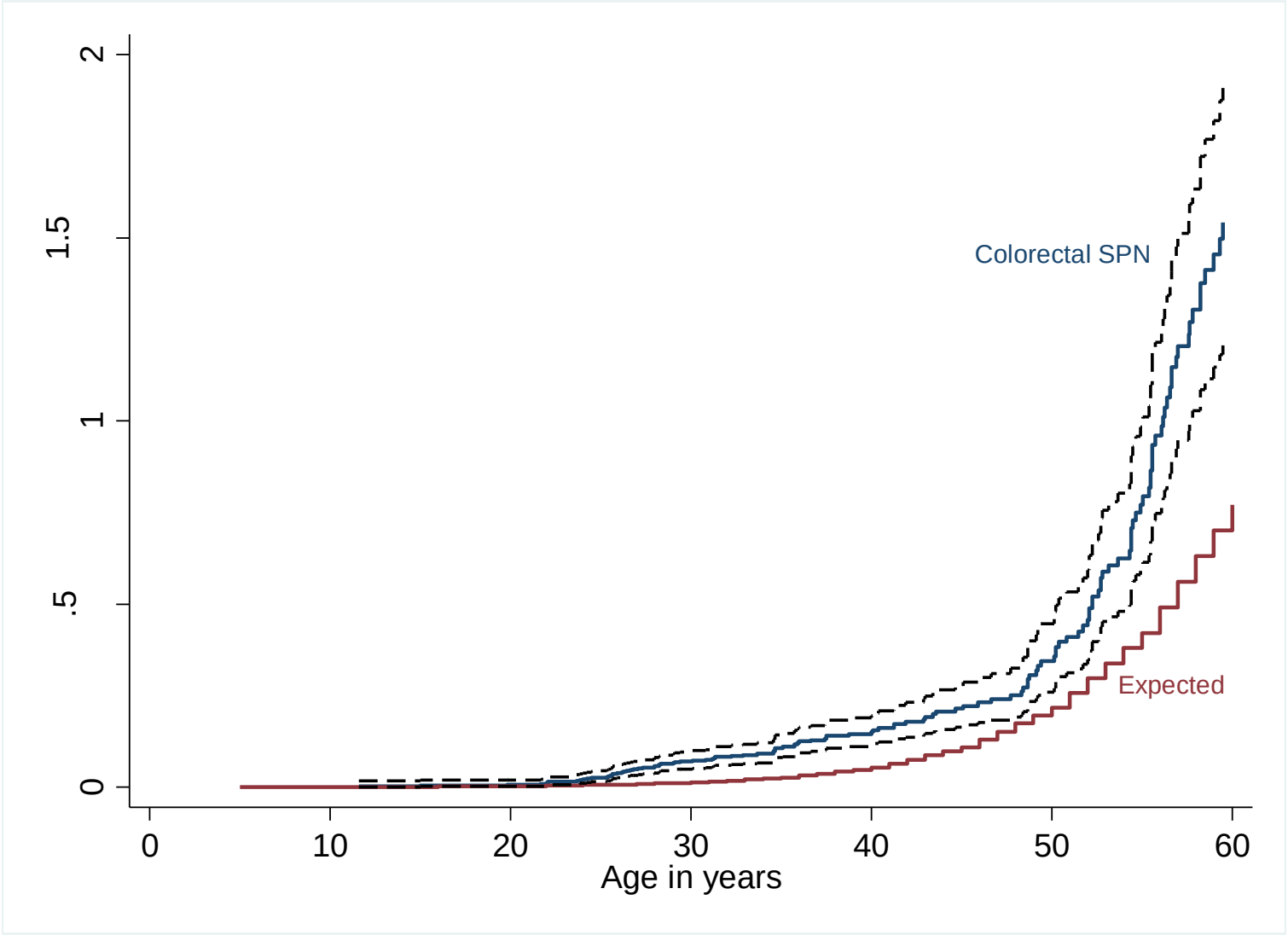


Figure 4.5.3 Cumulative incidence of developing a liver cancer among survivors with 95% confidence intervals and the corresponding cumulative incidence expected from the general population.

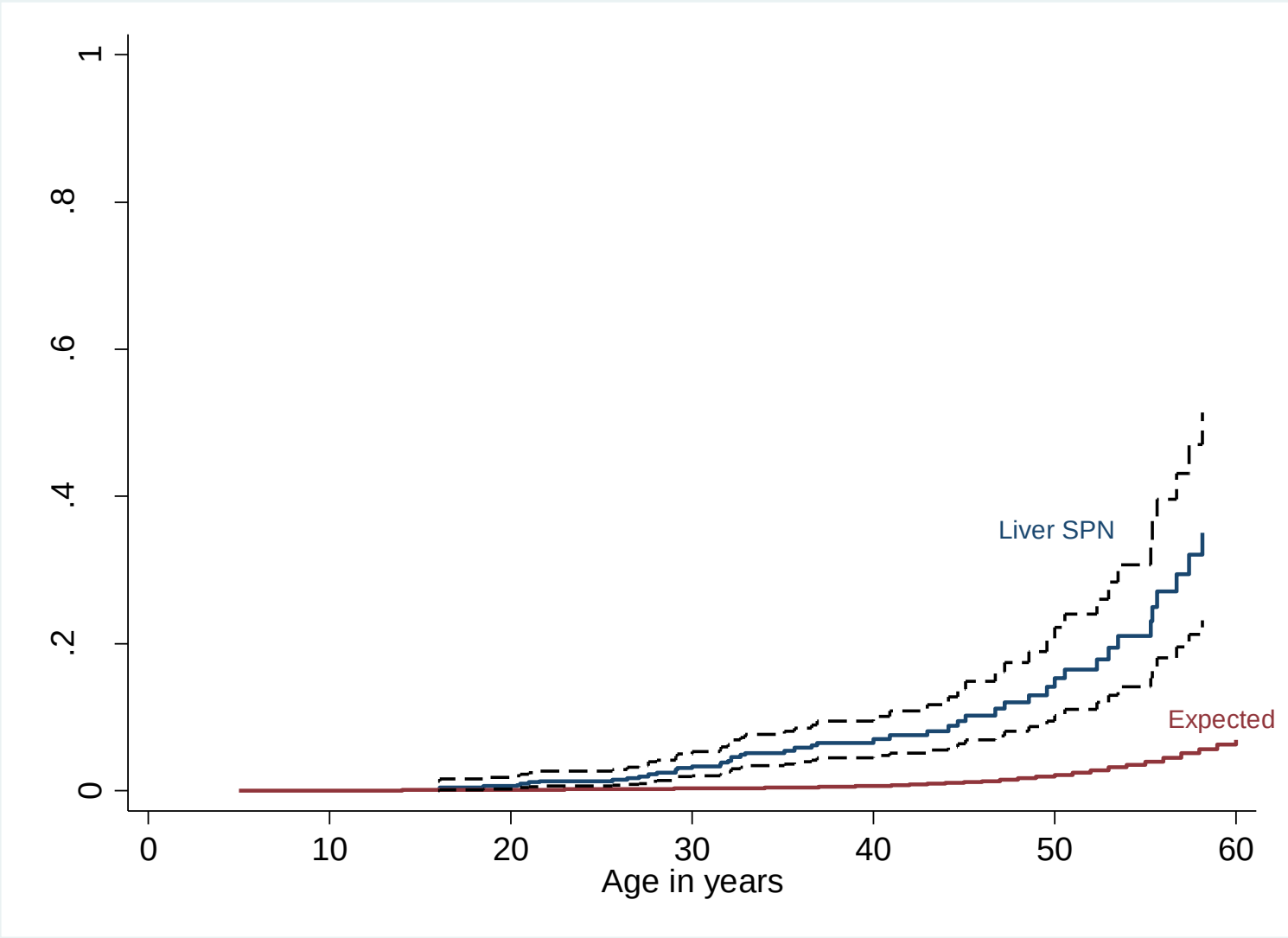


Figure 4.5.4 Cumulative incidence of developing a stomach cancer among survivors with 95% confidence intervals and the corresponding cumulative incidence expected from the general population.

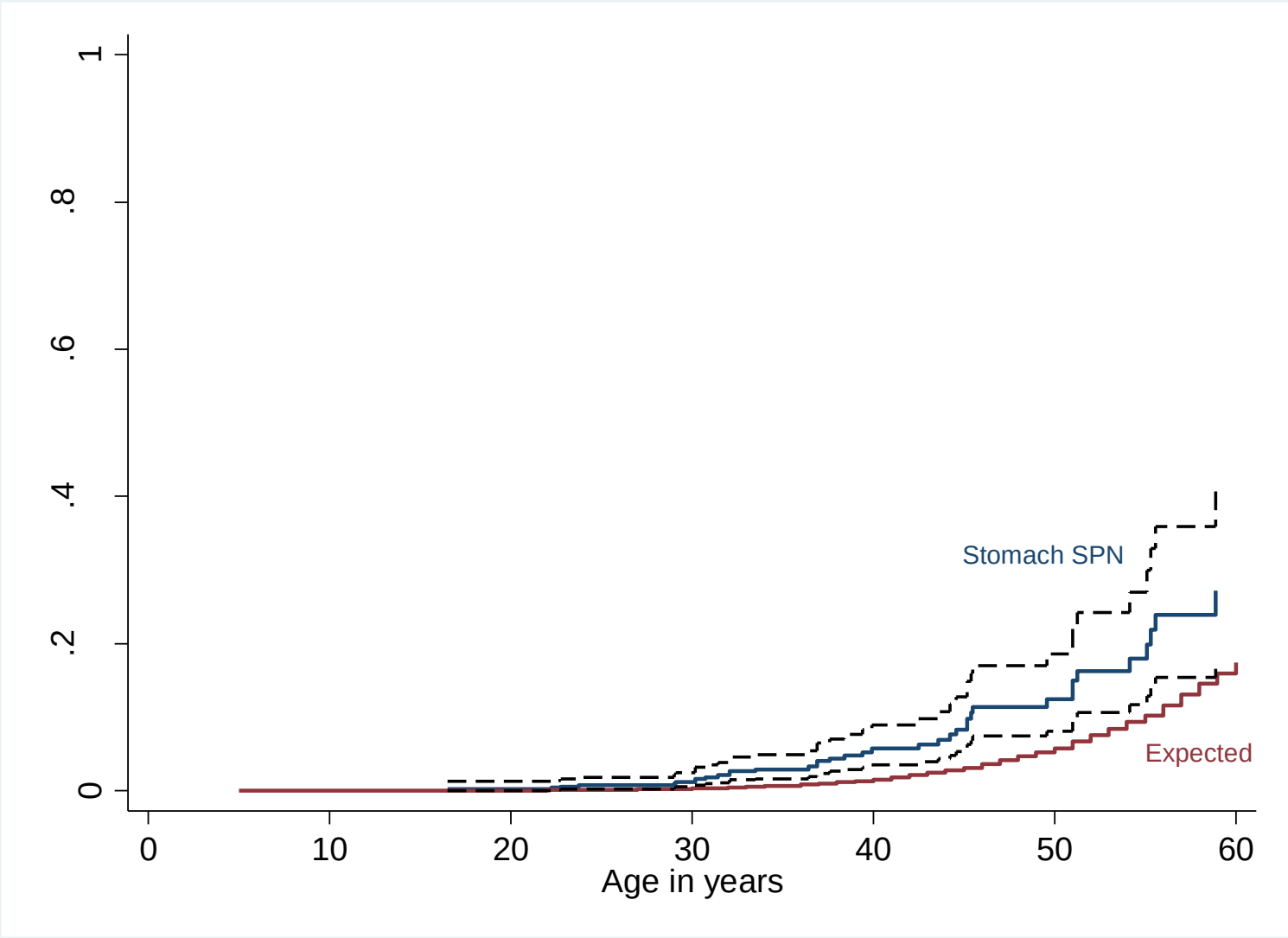


Figure 4.5.5 Cumulative incidence of developing a pancreatic cancer among survivors with 95% confidence intervals and the corresponding cumulative incidence expected from the general population.

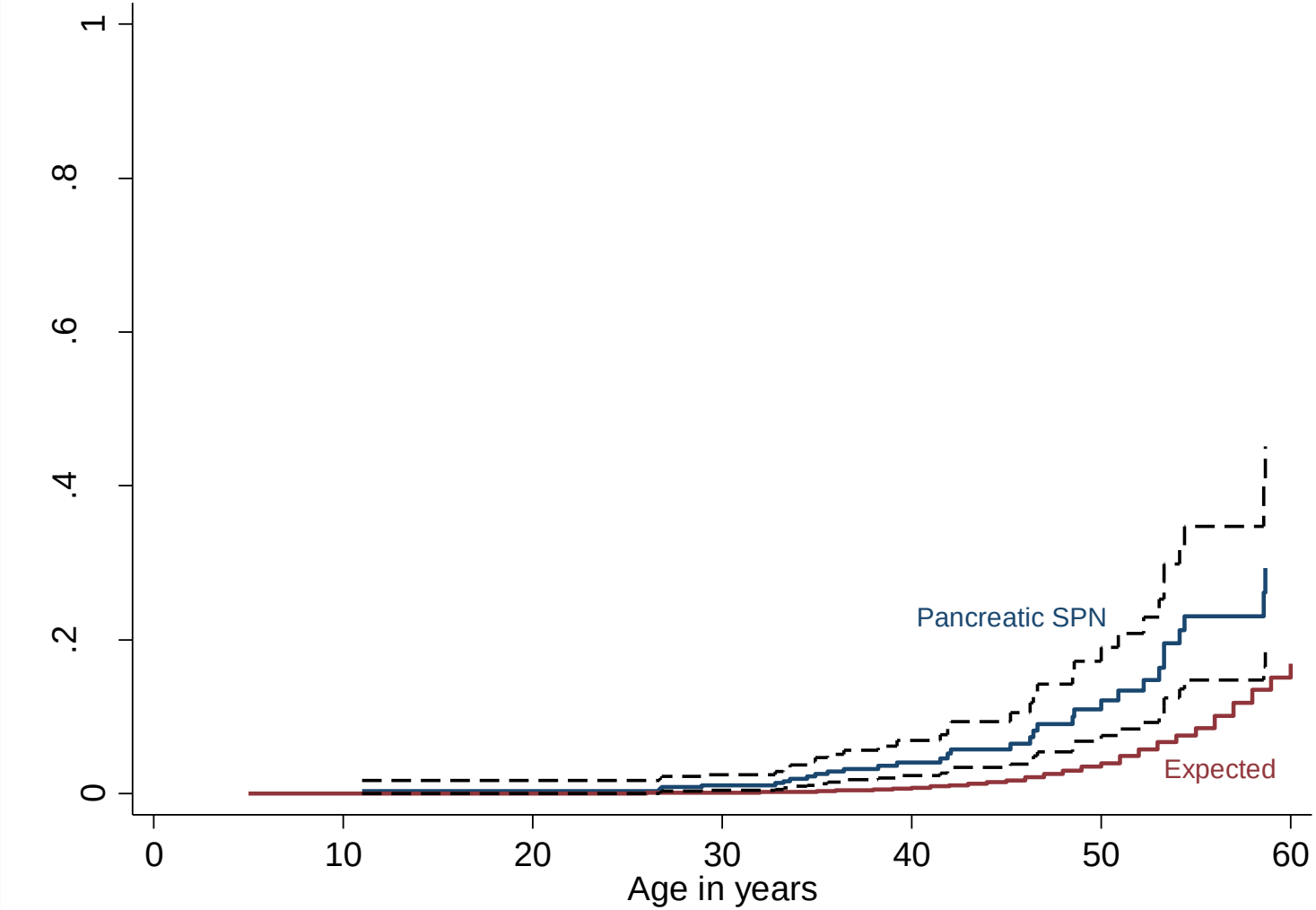


Figure 4.5.6 Cumulative incidence of developing a digestive SPN among Wilms' tumour survivors with 95% confidence intervals and the corresponding cumulative incidence expected from the general population.

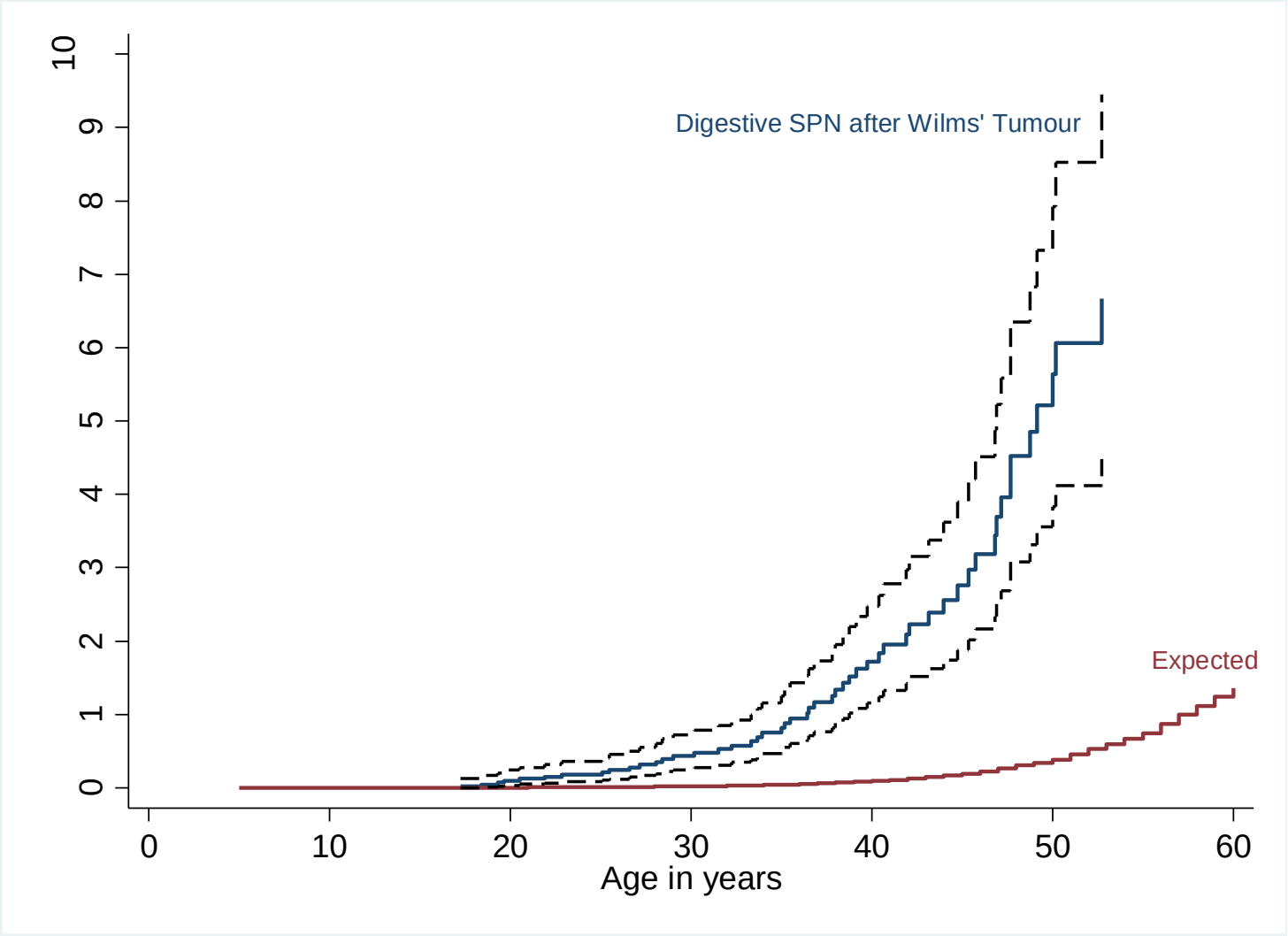
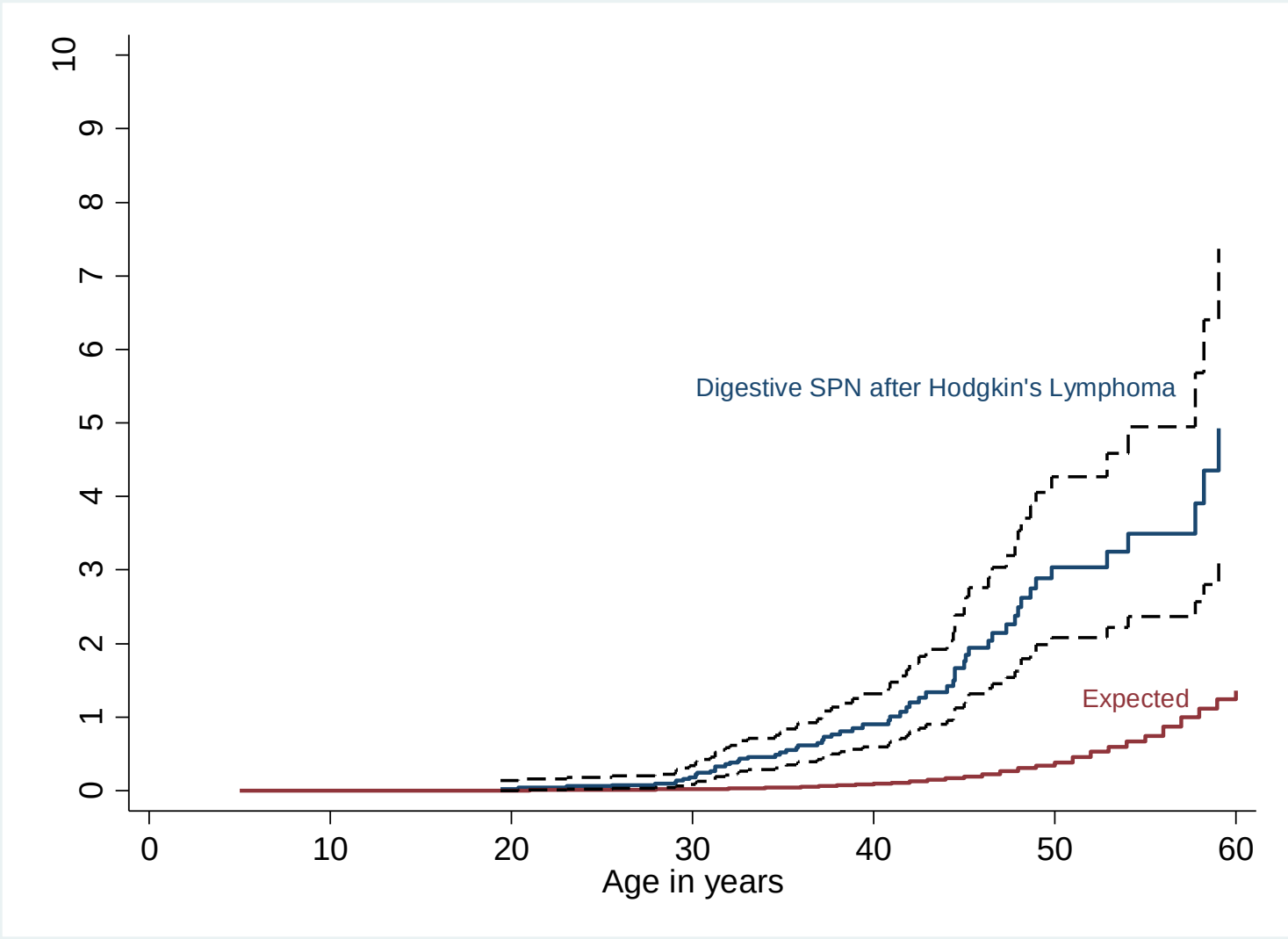


Figure 4.5.7 Cumulative incidence of developing a digestive SPN among Hodgkin's Lymphoma survivors with 95% confidence intervals and the corresponding cumulative incidence expected from the general population.



5 RISK OF ADVERSE HEALTH AND SOCIAL OUTCOMES BEYOND 50 YEARS AFTER HERITABLE RETINOBLASTOMA: THE BRITISH CHILDHOOD CANCER SURVIVOR STUDY.

Abstract

Background: Survivors of heritable retinoblastoma (HRb) are at long-term risk of adverse health and social outcomes; however, the risks of developing second primary neoplasms (SPN) due to radiotherapy remain uncertain. We investigated the risk of developing adverse health outcomes, including risk of developing SPNs, in relation to previous treatment with radiotherapy.

Patients and Methods: The British Childhood Cancer Survivor Study includes 552 five-year survivors of HRb. We investigated risks of SPNs, cause-specific mortality—and for those who completed a questionnaire—smoking status, educational achievement, health-status, adverse pregnancy outcomes and eye-related medical conditions. Risks were stratified by treatment with radiotherapy (none/beam/plaque) where possible.

Results: Overall, mortality was 8-times that expected (SMR=7.8; 95%CI: 6.6, 9.3). Cumulative mortality from all causes of death, excluding recurrence, was 26% at 50 years from diagnosis with 84% of excess deaths due to SPNs between 25–50 years from diagnosis. After 50 years from diagnosis, 59% of all excess deaths were attributable to SPNs. The risk of developing a bone SPN was over 300 times that expected (SIR=304.8; 95%CI: 214.6,420.1). Survivors who received external beam radiotherapy had a significantly higher risk of developing SPNs above the shoulder compared to no radiotherapy (SIR=4.0; 95%CI: 1.4,11.8).

Conclusion: HRb survivors, remain at an elevated risk of mortality beyond 25 years of follow up with SPN accounting for 84% of all excess deaths between 25-50 years of follow-up. Although the risk of developing an SPN was high, there was evidence of external beam radiotherapy increasing the risk of SPN above the shoulder. Current guidelines recommend long-term follow-up and screening for secondary

malignancies for all HRb survivors, but evidence from this study shows specific attention should be given to those who received external beam radiotherapy as part of their initial treatment.

5.1 Introduction

Retinoblastoma (Rb) is a rare type of childhood cancer developing in the eye in two forms: one heritable and one non-heritable. Heritable retinoblastoma is inherited as autosomal dominant with nearly complete penetrance and results from mutations in the RB1 tumour suppressor gene situated on chromosome 13[20]. Five-year survival after heritable retinoblastoma has improved substantially over recent decades from less than 70% in the 1970s to currently over 90%[23,24]. Although the vast majority of heritable retinoblastoma patients can expect to survive 5-years, survivors of heritable retinoblastoma are at a substantially increased risk of premature mortality and developing second primary neoplasms (SPNs)[205-207] compared to the general population.

Although a number of previous epidemiological studies investigated the risks of cause-specific mortality and risk of SPN[8,199,206-215] in heritable retinoblastoma survivors, few studies investigated other adverse health and social outcomes such as health-related quality of life, smoking behaviour, marriage and educational achievement. In addition, few studies investigated cause-specific mortality and risk of SPN by type of radiotherapy treatment received (i.e. by whether survivors received external beam radiotherapy, brachytherapy or no radiotherapy).

The principal objective of this population-based study was to investigate long-term risks of cause-specific mortality and subsequent primary neoplasms by specific type of radiotherapy treatment; and to investigate risks of adverse pregnancy outcomes; eye-related medical conditions; smoking status, alcohol consumption, educational

attainment, marriage; and health status among 5-year survivors of heritable retinoblastoma.

5.2 Methods

British Childhood Cancer Survivor Study (BCCSS)

The British Childhood Cancer Survivor Study (BCCSS) is a large-scale population-based cohort study investigating the long-term adverse health and social outcomes of childhood cancer and its treatment. The BCCSS consists of 17,980 survivors of childhood cancer—including 552 survivors of heritable retinoblastoma—who were diagnosed before 15 years of age, between 1940 and 1991 in Great Britain and survived for at least five years[154]. Patients with bilateral retinoblastoma or a family history of the disease were classified as heritable. The BCCSS cohort was ascertained through the National Registry of Childhood Tumours (NRCT).

Ascertainment of deaths and subsequent primary neoplasms

Ascertainment of deaths (including underlying cause of death) and SPNs in the BCCSS was achieved by individual patient electronic record linkage via the NHS Information Centre[216]. Confirmation of all SPNs was undertaken by writing to relevant clinician(s) to obtain all diagnostic reports to confirm site, type, and date of diagnosis, with particular reference to pathology reports[38].

BCCSS Questionnaire

All survivors who were alive and aged over 16 years were sent a 40-page questionnaire by their primary care physician on behalf of the BCCSS. In total, 298

(74%) of all eligible heritable retinoblastoma survivors (N=402) completed and returned the questionnaire[154]. The BCCSS questionnaire inquired about potential adverse health and social outcomes of childhood cancer and its treatment including questions regarding health-status (SF-36), health-care use, medical conditions, medical procedures, marriage, adverse pregnancy outcomes (e.g. miscarriage, stillbirth, preterm birth, abortion), smoking habits, alcohol consumption and educational achievements.

Ethical approval for the BCCSS was obtained from the relevant Multi-Centre Research Ethics Committee and every Local Research Ethics Committee in Britain (212 in total).

Statistical Analysis

Cause-Specific Mortality

To investigate cause-specific mortality, mortality rates of heritable retinoblastoma survivors in the BCCSS cohort were compared to mortality rates that would be expected based on the population of England & Wales. The period at risk of mortality began 5 years following initial diagnosis of childhood heritable retinoblastoma until the first occurrence of loss to death, follow up or exit date on 31st December 2014. Standardised mortality ratios (SMR) for specific causes of death were calculated by taking the ratio of observed over expected number of deaths for each cause. Absolute excess risks (AERs) were calculated by taking the observed minus expected number of deaths divided by the number of person-years at risk multiplied

by 10,000. Cumulative mortality for specific causes of death was estimated by treating other causes of death as competing risks[155].

Subsequent Primary Neoplasms

The period at risk of developing a SPN was initiated 5 years following initial diagnosis of childhood heritable retinoblastoma until the first occurrence of loss to follow up, death or exit date on 31st December 2006. Multiple SPNs per survivor were permitted for comparisons with the general population to avoid bias, but only the first SPN was considered in measures of cumulative risk. Standardised incidence ratios (SIRs), AERs and cumulative incidence of developing an SPN were calculated using the same methods as described above in relation to death. Risks of SPN were calculated by mode of radiotherapy treatment given and whether the SPN occurred above or below the shoulder.

Adverse Pregnancy Outcomes

To investigate the risks of adverse pregnancy outcomes, logistic regression models were used to calculate odds ratios (OR) for low birth weight, preterm births, abortion and miscarriage. Models were adjusted for maternal age and pregnancy order. Adverse pregnancy outcomes were investigated by comparing heritable retinoblastoma survivors to all other survivors in the BCCSS cohort who had had at least one completed pregnancy (N=6,593) (comparison with UK population pregnancy rates was not achievable as there is currently no database which holds information relating to the rates of adverse pregnancy outcomes).

Medical Conditions

To determine whether heritable retinoblastoma survivors were more prone to specific eye-related medical conditions after five-year survival, relative risks (RR) were calculated to compare heritable retinoblastoma survivors who did not receive surgery to survivors of all other cancers (N=10,190).

Health-status – *"Short Form 36"*

As part of the BCCSS questionnaire, functional health and well-being were measured by the SF-36 health-status questionnaire[54]. The SF-36 consists of eight measurement scales; physical function, role-physical, bodily pain, general health perception, mental health, role-emotional, social function and vitality. All eight SF-36 scores are measured on a scale from 0 to 100; with higher scores indicating more favourable outcomes. To compare SF-36 scale scores observed for heritable retinoblastoma survivors with a reference population, normative data from the Oxford Healthy Life Survey (OHLS) were used. The OHLS is a general population survey conducted between 1991 and 1992 that included 13,042 individuals aged 18-64 years randomly sampled from the Family Health Service Authority registers in Oxfordshire, Berkshire, Buckinghamshire and Northamptonshire. For each SF-36 scale, difference in mean scores between survivors of heritable retinoblastoma and OHLS was calculated using linear regression which adjusted for age and sex.

Smoking status, alcohol consumption and education level

Among those heritable retinoblastoma survivors who completed the BCCSS questionnaire, smoking and alcohol consumption and educational attainment were compared to the general population by using data from the nationwide General

Household Survey (GHS)[157]. Adjustment for confounders and classification of current regular smokers, alcohol consumption and educational attainment has been defined in previous BCCSS studies[51,61,64]. For each outcome, ORs comparing heritable retinoblastoma survivors to the GHS were calculated using multivariable logistic regression with a generalized estimating equation modification that took into account clustering within the GHS; these ORs were adjusted for attained age and sex.

Marital status

To investigate marital status among heritable retinoblastoma survivors, ORs of ever being married—stratified by sex and attained age—were calculated using data from the National Marriage Registry as the reference population[57]. Age-specific ORs were then pooled into one overall OR by using the Mantel-Haenszel method for combining ORs[158].

Statistical significance for all analyses was defined as a 2-sided $P<0.05$. All analyses were carried out in Stata 13 (StataCorp, College Station, Texas).

5.3 Results

Cohort Characteristics

From the total of 552 heritable retinoblastoma survivors in the cohort, 24.8% (N=137) had died, 1.1% (N=6) was lost to follow up and 74.1% (N=409) were alive at the exit date of the investigation (31st December 2014). Type of radiotherapy was split into survivors who received external beam radiotherapy (N=246)—defined as survivors

who only received external beam radiotherapy (N=164) and survivors who received mixed therapy (N=82)—and survivors who only received brachytherapy (N=129). Characteristics of heritable retinoblastoma survivors who completed the questionnaire were similar to all heritable retinoblastoma survivors in the BCCSS cohort (Table 5.5.1). But more males did not return the questionnaire compared to females and there was less follow-up in those who did not return the questionnaire, however, these factors were adjusted for in the analyses. Total follow-up of heritable retinoblastoma survivors in relation to mortality was 16,956 person-years following 5-year survival with mean and median follow-up of 30.7 and 31.1 years from heritable retinoblastoma diagnosis respectively with over 90% of the cohort still alive and under follow-up at 25 years after diagnosis.

Cause-Specific Mortality

Heritable retinoblastoma survivors experienced 8 times the number of deaths expected (SMR=7.8; 95%CI: 6.6, 9.3) with 64 additional deaths (95%CI: 51.9, 76.5) per 10,000 person-years in excess of that expected (Table 5.5.2). We focused on causes of death with at least 10 observations. Ignoring causes of death relating to recurrence, cause-specific mortality was highest for SPNs (SMR=18.2; 95%CI: 14.7, 22.4). In terms of the AER, the highest excess—with 72% of all excess deaths—was attributable to SPNs. Survivors who received external beam radiotherapy for their heritable retinoblastoma were more likely to die from an SPN (SMR=33.0; 95%CI: 24.2, 44.0) compared to those who received only brachytherapy (SMR=12.2; 95%CI: 7.9, 18.1) and those who did not receive any radiotherapy (SMR=12.6; 95%CI: 6.3, 22.6). The AER due to all causes of death other than recurrence was 33.0 excess deaths (per 10,000 person-years) between 0–25 years after heritable retinoblastoma

diagnosis, but increased 2-fold to 66.4 excess deaths in 25–50 years. During 25–50 years from heritable retinoblastoma diagnosis, causes of death other than recurrence or SPN only accounted for 15.7% of the excess number of deaths, whilst deaths due to SPNs alone accounted for 84.3% of the total number of excess deaths. Throughout the first 50 years of follow-up, no excess due to circulatory diseases was observed – however, post-50 years from diagnosis there were 65 excess deaths due to circulatory diseases per 10,000 survivors per year compared to the general population; although the observed number of deaths due to circulatory disease was only 3.

Cumulative mortality due to SPN and all other causes of death increased to 21.3% and 4.9% by 50 years after heritable retinoblastoma diagnosis respectively; cumulative mortality due to SPN and all other causes of death increased to 32.7% and 11.1% by 60 years after heritable retinoblastoma respectively (Figure 5.5.1).

Subsequent Primary Neoplasms

Heritable retinoblastoma survivors experienced over 13 times the number of SPNs expected (SMR=13.6; 95%CI: 11.2, 16.3) with 70 additional SPNs (95%CI: 56.3, 83.9) per 10,000 person-years in excess of that expected (Table 5.5.3). Survivors who received external beam radiotherapy had a significantly higher cumulative incidence of SPNs compared to those who received brachytherapy and those who did not receive radiotherapy (P=0.03) (Figure 5.5.2). The cumulative incidence of developing an SPN was 12.5%, 8.0% and 7.0% by 25 years for survivors who received external beam radiotherapy, brachytherapy and no radiotherapy respectively. These percentages increased to 43.0%, 34.0% and 39.5% by 50 years

respectively. The most common SPN was of bone sites, which occurred in 35 heritable retinoblastoma survivors. The overall number of excess bone SPNs was 24 (95%CI: 16.4, 32.1) per 10,000 person-years. However, the excess risk of bone SPNs was mainly between 5–20 years of follow-up; after 30 years from diagnosis, the number of excess cases of bone SPNs dropped to zero (Figure 5.5.3). The excess risk of SPNs of sites other than bone increases rapidly after 25 years from diagnosis and reached 134.5 excess cases of SPNs per 10,000 person-years compared to the general population – this is equivalent to 1.3% excess cases of SPN observed in survivors compared to the general population per year. Overall, heritable retinoblastoma survivors who received external beam radiotherapy had a marginal significantly increased risk of SPN compared to survivors who had no radiotherapy (RR=1.6; 95%CI: 1.0, 2.5). When stratifying by location of the SPN (above shoulder and below shoulder), survivors who received external beam radiotherapy had a 4-fold risk (RR=4.0; 95%CI: 1.4, 11.8) of SPN developing above the shoulder compared to those who did not receive any radiotherapy (Table 5.5.4).

Medical Conditions

Of those who returned the questionnaire and did not have surgery (which would likely be enucleation of the eye, N=23), over a quarter ended up blind (27.3%), over half developed cataracts (60.9%) and over half developed detached retinas (60.9%). The respective percentage of survivors who received radiotherapy prior to developing these conditions was 100%, 100% and 86%. Overall, heritable retinoblastoma survivors were 6-times more likely to be blind (RR=6.4; 95%CI: 5.7, 7.1), 17-times more likely to develop cataracts (RR=17.0; 95%CI: 16.7, 17.3) and 28-times more

likely to have a detached retina (RR=28.4; 95%CI: 28.0, 28.8) compared to survivors of all other cancers (Table 5.5.5).

Pregnancy Outcomes

Of the 298 heritable retinoblastoma survivors who completed the BCCSS questionnaire, 91 reported that themselves, or their partners, had been pregnant at least once and they produced 191 completed pregnancies. From 191 pregnancies, 13.6% were aborted and 12.2% resulted in a miscarriage. Pregnancies of survivors of heritable retinoblastoma were no more likely to result in low birth weight (OR=0.6; 95%CI: 0.3, 1.4), premature birth (OR=0.6; 95%CI: 0.3, 1.2), abortion (OR=1.2; 95%CI: 0.8, 2.0) and no different in miscarriage (OR=0.8; 95%CI: 0.5, 1.3) compared to pregnancies from childhood cancer survivors which were not diagnosed with heritable retinoblastoma.

Educational Attainment, Smoking and Marriage

Heritable retinoblastoma survivors were more likely to obtain a degree (OR=1.8; 95%CI: 1.4, 2.4), teaching qualification (OR=1.4; 95%CI: 1.1, 1.9), A-Level (OR=1.4; 95%CI: 1.0, 1.8) and O-Level (OR=1.5; 95%CI: 1.1, 2.1) compared to the general population. Survivors were also less likely to be a regular smoker (OR = 0.5; 95%CI: 0.4, 0.7) than the general population. Both male (OR = 0.5; 95%CI: 0.3, 0.7) and female (OR = 0.4; 95%CI: 0.3, 0.6) heritable retinoblastoma survivors were substantially less likely to be married compared to the general population.

Health Status (SF-36)

Heritable retinoblastoma survivors scored significantly lower than the general population on two of the eight SF-36 scales; role-physical (difference in means, D=–4.6; 95%CI: –8.2, –1.1) and social functioning (D=–2.5; 95%CI: –4.8, –0.1). However, heritable retinoblastoma survivors reported significantly better vitality (D=4.0; 95%CI: 1.7, 6.3) than the general population.

5.4 Discussion

This is the first population-based study to assess the risk of SPNs by external beam radiotherapy and brachytherapy for heritable retinoblastoma survivors. Survivors of heritable retinoblastoma had a significantly higher risk of developing SPNs, specifically bone tumours in the first 25 years of follow-up and soft tissue sarcomas, digestive, genitourinary and breast carcinomas after 25 years of follow up, and an overall annual risk of 1.3% between 25-50 years of follow-up. Most survivors, with known treatment received radiotherapy (84%). Survivors were significantly more likely to develop a SPN and, specifically, over 300 times more likely to develop a bone SPN which is consistent with previous studies[38,205,208,213,214,217,218]. Similar to a previous study, we found significant evidence of radiotherapy, specifically external beam radiotherapy, increasing the risk of developing SPN[199]. When examining specific types of radiotherapy, the risk of SPNs developing above the shoulder due to external beam radiotherapy was 4-fold that compared to those who did not receive any radiotherapy; the risk was not increased for SPNs occurring below the shoulder (p=0.58). The risk of developing SPNs for those who received brachytherapy was comparable to those who did not receive any radiotherapy (p=0.62). We conclude

that external beam radiotherapy is a cause of SPNs, specifically above the shoulder, with the possibility of influence of other genetic factors – a previous study found significantly increased risks of specific types of RB1 gene mutation on the development of SPNs[219].

Similar to previous studies, survivors were at risk of premature mortality, particularly due to SPNs and recurrences; these causes of death account for 72% and 13% of the total excess risk respectively[8,209,215,220]. Excess deaths due to SPNs within 25 years of follow up accounted for 68% of the total excess death but this increased to 84% for 25–50 years of follow up indicating a large majority of excess deaths were attributable to second cancers after 25 years of follow up. When examining deaths due to SPNs by different radiotherapy types, a significantly higher SMR was observed for those who received external beam radiotherapy compared to those who received brachytherapy for their initial heritable retinoblastoma. In fact, mortality due to SPN for those who received brachytherapy for their initial heritable retinoblastoma was comparable to those who did not receive any radiotherapy.

Heritable retinoblastoma survivors who did not undergo surgery, and hence unlikely to have their eyes enucleated, were significantly more likely to be blind, develop cataracts and develop a detached retina compared to other cancer survivors. Previous studies also reported significantly higher radiation induced cataracts in retinoblastoma survivors compared to no irradiation, however external beam radiotherapy was given much more commonly in previous studies (87% of patients in US compared to 45% in our UK study)[221-223].

Pregnancies from heritable retinoblastoma survivors were no more likely to be underweight, premature, aborted or miscarried compared to other cancer survivors. A previous study detailed that those with heritable retinoblastoma reproduce at age similar to the general population and with a 50% chance of passing on the mutated RB1 allele with each pregnancy[20]. Although it is not known how many survivors were fully aware of their condition and its heritability aspect, it is vital that survivors are made aware of their hereditary condition or receive genetic counselling.

With respect to social outcomes, and consistent with previous studies, heritable retinoblastoma survivors appear to lead a healthier lifestyle being less likely a regular smoker than the general population[61,224]. Survivors were significantly more likely to attain educational qualifications compared to the general population but were less likely to be married compared to the general population with only 38% of survivors who completed the questionnaire being married[51,57].

A previous study has shown that survivors of heritable retinoblastoma reported adverse health-status outcomes similar to our study, that is, lower role-physical and heightened vitality. However, social function is comparable to the general population and heritable retinoblastoma survivors had a significantly lower perception of their general health[225].

An existing guideline recommends survivors of heritable retinoblastoma to be actively screened for eye-related medical conditions and after five years, screening for secondary cancers every one to two years and eye-related medical conditions every two to three years[226]. This study provides evidence that survivors should remain on

long-term follow-up, as the risk of developing a SPN is significantly higher than the general population. Further investigation into the specific type of radiotherapy treatment revealed that survivors who have received external beam radiotherapy had a significantly higher risk of SPNs, compared to those who didn't receive radiotherapy, developing above the shoulder. As nearly half (N=246/552) of our heritable retinoblastoma survivors received external beam radiotherapy, it should be considered that, during long-term follow-up, special attention should be given to those who have received external beam radiotherapy than those who received brachytherapy or did not receive any radiotherapy.

Study Limitations

A potential limitation of our study included the lack of detailed doses on radiotherapy and chemotherapy exposures given for heritable retinoblastoma. It is important to acknowledge that survivors included in the cohort were treated between 1940 and 1991 and hence findings may not be generalisable to survivors treated in more recent years due to changes in exposure to different treatments – currently, radiotherapy is given less frequently as part of the initial treatment plan for retinoblastoma[214]. Despite the lack of treatment information, long-term risks can be estimated in ageing survivors of heritable retinoblastoma.

Conclusion

In conclusion, survivors of heritable retinoblastoma lead a healthier lifestyle by being less likely a smoker and more likely to achieve educational qualifications but feel

significantly more limited than the general population in certain tasks, most likely, due to their impaired sight. This may also be the reason for their significantly reduced social functioning. Survivors of heritable retinoblastoma are at increased risk of premature mortality especially due to second malignancies – after 25 years of follow up, almost all excess deaths were due to second malignancies. The risk of second malignancies are high, especially bone in the first 25 years from initial diagnosis, which seems to be driven by external beam radiotherapy, but the risk of other cancers such as soft tissue sarcoma, digestive, genitourinary, breast carcinoma are especially high after 25 years from initial diagnosis. Current guidelines recommend long-term follow-up and screening for secondary malignancies for all heritable retinoblastoma survivors, but evidence from this study shows that specific attention should be given to those who received external beam radiotherapy as part of their initial treatment.

5.5 Tables and Figures

Table 5.5.1. Characteristics of all 552 Heritable Retinoblastoma (HRb) survivors in the British Childhood Cancer Survivor Study and of all those who completed a questionnaire.

		All HRb Survivors (N = 552)	Completed Questionnaire Returned (N = 298)	No Completed Questionnaire Returned (N = 254)
Sex	Male	300 (54.4%)	149 (50.0%)	151 (59.5%)
	Female	252 (45.6%)	149 (50.0%)	103 (41.5%)
Age at Diagnosis (years)	Mean	1.1	1.2	0.9
	< 1	332 (60.1%)	169 (56.7%)	163 (64.2%)
	1 – 14	220 (39.9%)	129 (43.3%)	91 (35.8%)
Age at Questionnaire Completion[1] (Years)	Mean	n/a	40.5	n/a
	5 – 14	n/a	0 (0.0%)	n/a
	15 – 24	n/a	34 (11.4%)	n/a
	25 – 34	n/a	68 (22.8%)	n/a
	35 – 44	n/a	87 (29.2%)	n/a
	45 – 54	n/a	70 (23.5%)	n/a
	55 – 64	n/a	35 (11.7%)	n/a
	65+	n/a	4 (1.3%)	n/a
Follow up since HRb diagnosis[2] (years)	5-14	23 (4.2%)	0 (0.0%)	23 (9.1%)
	15-24	29 (5.3%)	1 (0.3%)	28 (11.0%)
	25-34	101 (18.3%)	49 (16.4%)	52 (20.5%)
	35-44	133 (24.1%)	76 (25.5%)	57 (22.4%)
	45+	266 (48.2%)	172 (57.7%)	94 (37.0%)
Treated with Radiotherapy	Yes	419 (75.9%)	216 (72.5%)	203 (79.9%)
	No	81 (14.7%)	50 (16.8%)	31 (12.2%)
	Missing	52 (9.4%)	32 (10.7%)	20 (7.9%)
Treated with Specific Radiotherapy[3]	External Beam	164 (29.7%)	78 (26.2%)	86 (33.9%)
	Brachytherapy	129 (23.4%)	73 (24.5%)	56 (22.0%)
	Mixed Therapy	82 (14.9%)	42 (14.1%)	40 (15.7%)
	No Radiotherapy	81 (14.7%)	50 (16.8%)	31 (12.2%)
	Missing	96 (17.4%)	55 (18.5%)	41 (16.1%)
Treated with Chemotherapy	Yes	74 (13.4%)	37 (12.4%)	37 (14.6%)
	No	351 (63.6%)	185 (62.1%)	166 (65.4%)
	Missing	127 (23.0%)	76 (25.5%)	51 (20.0%)
Surgery	Yes	337 (61.1%)	186 (62.4%)	151 (59.5%)
	No	51 (9.2%)	23 (7.7%)	28 (11.0%)
	Missing	164 (29.7%)	89 (29.9%)	75 (29.5%)

[1] The BCCSS questionnaire was sent out to survivors aged 16 or over.
[2] Years of follow-up after initial diagnosis; percentages correspond to the total number in cohort or completed questionnaire.
[3] Proportion of those who received radiotherapy and missing treatment information. External Beam denotes survivors who only received External Beam Radiotherapy. Brachytherapy denotes survivors who only received a plaque. Mixed Therapy denotes survivors who received both External Beam Radiotherapy and Brachytherapy.

Table 5.5.2. Cause-specific standardised mortality ratios (SMRs) and absolute excess risks (AERs) for survivors of Heritable Retinoblastoma.

Cause†	Obs/Exp	SMR (95% CI)	AER (95% CI)	% of Total AER	0–25 Years‡		25–50 Years‡		50+ Years‡	
					Observed	AER (%)	Observed	AER (%)	Observed	AER (%)
All Causes	137/17.5	7.8 (6.6 , 9.3)	64.2 (51.9 , 76.5)	100%	62	44.5 (100%)	54	66.4 (100%)	21	465.4 (100%)
Neoplasm	117/5.0	23.4 (19.4 , 28.1)	60.2 (48.8 , 71.6)	94%	56	42.3 (95.0%)	45	65.6 (98.7%)	16	368.3 (79%)
Recurrence	15/–	–	8.1 (3.5, 12.6)	13%	15	11.5 (25.8%)	0	0 (0%)	0	0 (0%)
SPN	91/5.0	18.2 (14.7 , 22.4)	46.2 (36.2 , 56.2)	72%	40	30.1 (67.6%)	39	56.0 (84.3%)	12	273.4 (58.7%)
Any Radiotherapy	76/3.9	19.3 (15.2 , 24.1)	50.6 (38.6 , 62.6)	NA¥	34	36.7 (NA)	33	74.3 (NA)	9	508.4 (NA)
Plaque Only	25/2.0	12.2 (7.9 , 18.1)	43.0 (24.6 , 61.3)	NA¥	14	28.1 (NA)	11	32.3 (NA)	0	0 (NA)
External Beam	46/1.4	33.0 (24.2 , 44.0)	59.5(41.7 , 77.2)	NA¥	25	47.1 (NA)	17	95.4 (NA)	4	996.8 (NA)
No Radiotherapy	11/0.9	12.6 (6.3, 22.6)	34.4 (12.3 , 56.5)	NA¥	4	20.5 (NA)	4	41.0 (NA)	3	663.2 (NA)
Nervous	2/0.8	2.6 (0.3 , 9.5)	0.7 (–0.8 , 2.2)	1%	2	1.4 (3.1%)	0	–0.8 (–1.2%)	0	–1.2 (–0.3%)
Circulatory	5/2.9	1.7 (0.6, 4.0)	1.1 (–1.2 , 3.5)	2%	0	–0.3 (–0.6%)	2	–0.5 (–0.8%)	3	64.6 (13.9%)
Respiratory	4/0.9	4.3 (1.2 , 10.9)	1.6 (–0.5 , 3.8)	2%	2	1.4 (3.2%)	1	0.4 (0.7%)	1	21.9 (4.7%)
Digestive	3/1.2	2.5 (0.5 , 7.4)	1.0 (–0.9, 2.8)	2%	1	0.6 (1.4%)	1	0.1 (0.2%)	1	21.5 (4.6%)
Genitourinary	1/0.1	7.6 (0.2 , 42.5)	0.5 (–0.6, 1.5)	1%	0	–0.0 (–0.0%)	1	1.4 (2.2%)	0	–0.3 (–0.1%)
Other	1/0.2	5.9 (0.1, 32.8)	0.4 (–0.6, 1.5)	1%	0	–0.4 (–1.0%)	1	–0.2 (–0.2%)	0	–2.5 (–0.5%)
External	2/4.8	0.4 (0.1 , 1.5)	–1.5 (–3.0 , 0.0)	–2%	1	–0.5 (–1.1%)	1	–2.9 (–4.4%)	0	–6.7 (–1.4%)

Calculation of SMR for deaths due to recurrence of HRb would not be appropriate since the expected mortality rate in the general population would be 0. AER for recurrence was calculated as the incidence rate per 10,000 person-years. Confidence intervals were calculated using the approximate method where the number of deaths≥100 and the Poisson exact method where number of deaths<10. † All causes of death presented as overall SMR, AER and also by years of follow up. Eleven causes of death classified as neoplastic but is unknown with regards to recurrence or SPN. Neoplasm comprises recurrence and SPNs and circulatory comprises cardiac and stroke. 2 causes of death were unknown. ‡ Numbers at risk: (0–25 Years: 552), (25–50 Years: 461) and (50+ Years: 127). ¥ Mortality due to SPN by modes of treatment was analysed as subgroups and not respective to total.

Table 5.5.3. SIRs and AERs for developing specific SPNs after Heritable Retinoblastoma.

Second Primary Cancer	Overall			0–24 years from diagnosis		25–50 years from diagnosis	
	Obs/Exp	SIR (95%CI)	AER (95%CI)[1]	SIR (95%CI) (N)	AER (95%CI)[1]	SIR (95%CI) (N)	AER (95%CI)[1]
All	115/8.4	13.6 (11.2-16.3)	70.1 (56.3-83.9)	24.4 (18.5-31.6) (57)	47.9 (34.9-60.9)	9.5 (7.2-12.3) (58)	137.1 (97.6-176.5)
Bone	37/0.1	304.8 (214.6-420.1)	24.3 (16.4-32.1)	356.2 (249.5-493.2) (36)	31.5 (21.2-41.8)	49.1 (1.2-273.7) (1)	2.6 (-2.6-7.8)
Soft Tissue	16/0.1	117.1 (66.9-190.1)	10.4 (5.3-15.6)	38.4 (7.9-112.1) (3)	2.6 (-0.4-5.5)	222.3 (118.4-380.2) (13)	34.2 (15.5-52.8)
Genitourinary	15/1.9	7.9 (4.4-13.0)	8.6 (3.6-13.6)	1.9 (0.0-10.5) (1)	0.4 (-1.3-2.1)	10.3 (5.6-17.2) (14)	33.4 (14.0-52.7)
Digestive	11/0.9	12.5 (6.2-22.4)	6.7 (2.4-10.9)	31.2 (6.4-91.3) (3)	2.5 (-0.4-5.5)	10.2 (4.4-20.1) (8)	19.1 (4.4-33.7)
Breast	9/1.9	4.7 (2.1-8.9)	4.7 (0.8-8.5)	24.1 (5.0-70.4) (3)	24.1 (5.0-70.4)	3.3 (1.2-7.3) (6)	11.1 (-1.6-23.8)

[1]AER per 10,000 person–years.

Table 5.5.4. Effect of radiotherapy on risk of developing an SPN presented as Risk Ratios (RR).

		RR (95%CI)	P-value
All sites	No RT	1.0 (ref.)	
	Plaque	0.9 (0.5,1.5)	0.62
	Beam	1.6 (1.0,2.5)	0.05
Bone	No RT	1.0 (ref.)	
	Plaque	1.1 (0.4,2.8)	0.91
	Beam	1.6 (0.7,3.5)	0.28
Soft-tissue	No RT	1.0 (ref.)	
	Plaque	0.8 (0.2,3.2)	0.80
	Beam	1.5 (0.4,5.3)	0.51
Above Shoulder	No RT	1.0 (ref.)	
	Plaque	2.6 (0.8,8.2)	0.09
	Beam	4.0 (1.4,11.8)	0.01
Below Shoulder	No RT	1.0 (ref.)	
	Plaque	0.6 (0.3,1.1)	0.1
	Beam	1.2 (0.7,2.0)	0.58

Table 5.5.5. Risk of developing eye-related medical conditions after five-year survival compared to survivors of other cancers.

	H-Retinoblastoma, N (%)	Other Cancer Survivors, N (%)	Relative Risk	95% Confidence Interval
Blindness†	6 / 22 (27.3%)	429 / 10,013 (4.3%)	6.4	(5.7 – 7.1)
Cataracts†	14 / 23 (60.9%)	360 / 10,031 (3.6%)	17.0	(16.7 – 17.3)
Detached Retina†	14 / 23 (60.9%)	214 / 9,978 (2.1%)	28.4	(28.0 – 28.8)

†Comparisons for Heritable Retinoblastoma who did not received surgery compared with all other cancer survivors. Numbers relate to survivors of heritable retinoblastoma who did not receive surgery and to survivors of all other cancers, of who did not previously have the event and answered the relevant questions on the questionnaire.

Table 5.5.6. Odds Ratios (Ors) of pregnancy outcomes, smoking status, educational level and marital status.

	N (%)	OR (95%CI)
Education (Achievement)[1]		
Degree	73 / 229	1.8 (1.4 – 2.4)
Teaching Qualification	91 / 229	1.4 (1.1 – 1.9)
A-Level	135 / 243	1.4 (1.0 – 1.8)
O-Level	230 / 289	1.5 (1.1 – 2.1)
Smoking[2]		
Current Regular Smokers	47 / 294 (16.0%)	0.5 (0.4 – 0.7)
Alcohol Consumption[3]		
Current Drinker	230 / 297 (77.4%)	0.5 (0.3 – 0.6)
Over Recommendation	45 / 228 (19.7%)	0.6 (0.4 – 0.8)
Harmful Doses	3 / 228 (1.3%)	0.2 (0.1 – 0.6)
Pregnancy Outcome[4]		
Low Birth Weight	9 / 124 (7.3%)	0.6 (0.3 – 1.4)
Preterm Birth	15 / 136 (11.0%)	0.6 (0.3 – 1.2)
Abortion	26 / 191 (13.6%)	1.2 (0.8 – 2.0)
Miscarriage	23 / 189 (12.2%)	0.8 (0.5 – 1.3)
Pregnancy Outcome (F)[4]		
Low Birth Weight	5 / 77 (6.5%)	0.5 (0.2 – 1.5)
Preterm Birth	8 / 81 (9.9%)	0.5 (0.2 – 1.2)
Abortion	16 / 113 (14.2%)	1.2 (0.7 – 2.1)
Miscarriage	13 / 112 (11.6%)	0.7 (0.4 – 1.2)
Pregnancy Outcome (M)[4]		
Low Birth Weight	4 / 47 (8.5%)	0.8 (0.2 – 3.1)
Preterm Birth	7 / 55 (12.7%)	0.7 (0.2 – 2.1)
Abortion	10 / 78 (12.8%)	1.4 (0.6 – 3.3)
Miscarriage	10 / 77 (13.0%)	1.1 (0.5 – 2.4)
Marital Status[5]		
Males	50 / 147 (34.0%)	0.5 (0.3 – 0.7)
Females	62 / 149 (41.6%)	0.4 (0.3 – 0.6)

†Odds ratios were pooled using Mantel-Haenszel method.
[1] adjusted for, sex and attained age.
[2] adjusted for sex, attained age, marital status, socioeconomic classification, educational attainment.
[3] controlled for attained age, sex, legal marital status, socioeconomic classifications, educational attainment, and region, and took into account the GHS weighting factor, for the likelihood of consuming over the recommendations for weekly alcohol units or consuming harmful weekly amounts of alcohol.
[4] HRb survivors compared against non-Rb survivors. (F) denotes pregnancies from female survivors and (M) denotes pregnancies from partners of male survivors.
[5] compared to British population marriage statistics from ONS 2002.

Table 5.5.7. Differences in mean SF–36 scores between Heritable Retinoblastoma survivors and OHLS reference population.

SF-36 Scale	Difference in mean (95%CI)[1]
Reported Health Change	–1.2 (–3.1, 0.6)
Physical Function	–0.7 (– 2.8, 1.3)
Role–Physical	–4.6 (–8.2, –1.1)
Role–Emotional	–0.2 (–4.0, 3.5)
Social Functioning	–2.5 (–4.8, –0.1)
Mental Health	1.1 (–0.9, 3.1)
Vitality	4.0 (1.7, 6.3)
Bodily Pain	1.6 (–0.9, 4.2)
General Health Perception	1.1 (–1.2, 3.4)

[1] Calculated scores were adjusted for age and sex.

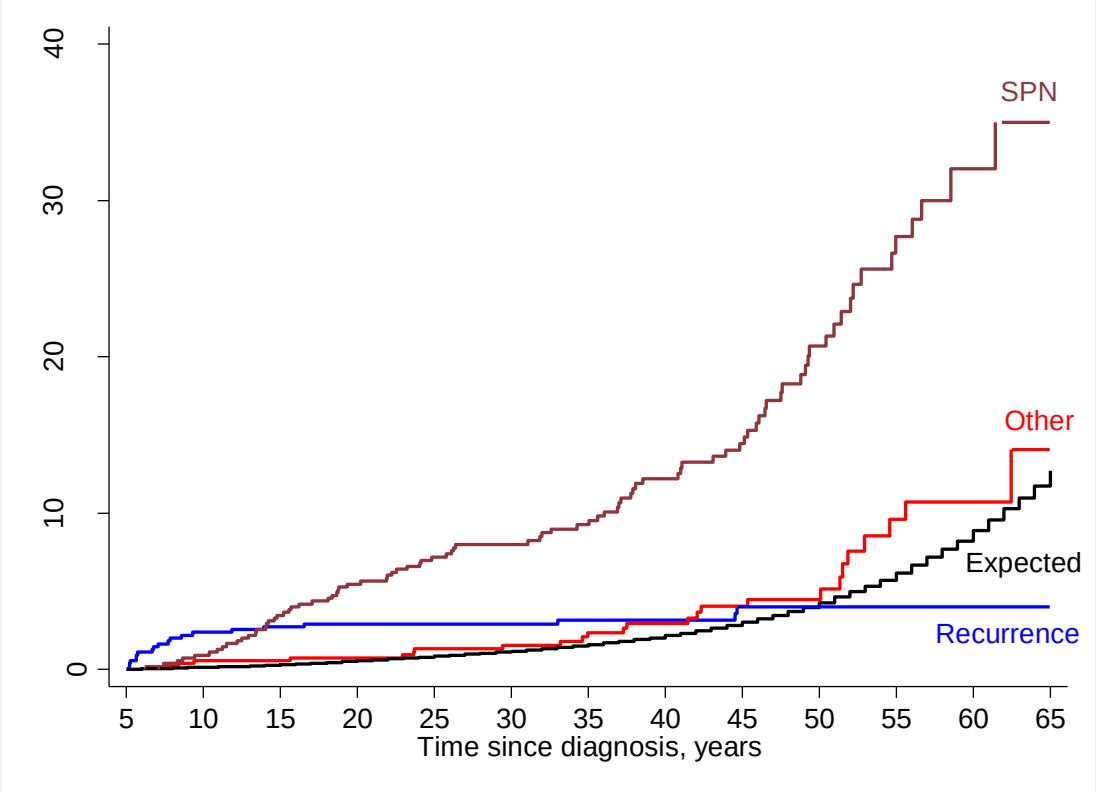


Figure 5.5.1. Cumulative mortality stratified by causes of death; SPN, Recurrence, Other Causes and All Cause Expected.

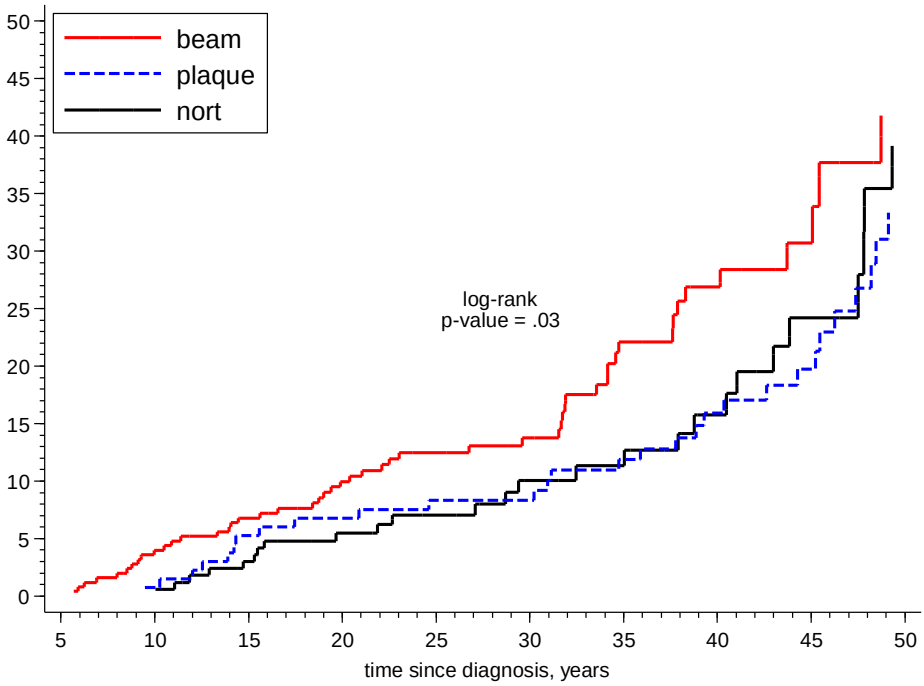


Figure 5.5.2. Cumulative incidence of developing an SPN among heritable retinoblastoma survivors according to whether treatment involved external beam radiotherapy (beam), brachytherapy (plaque) or no radiotherapy (nort).

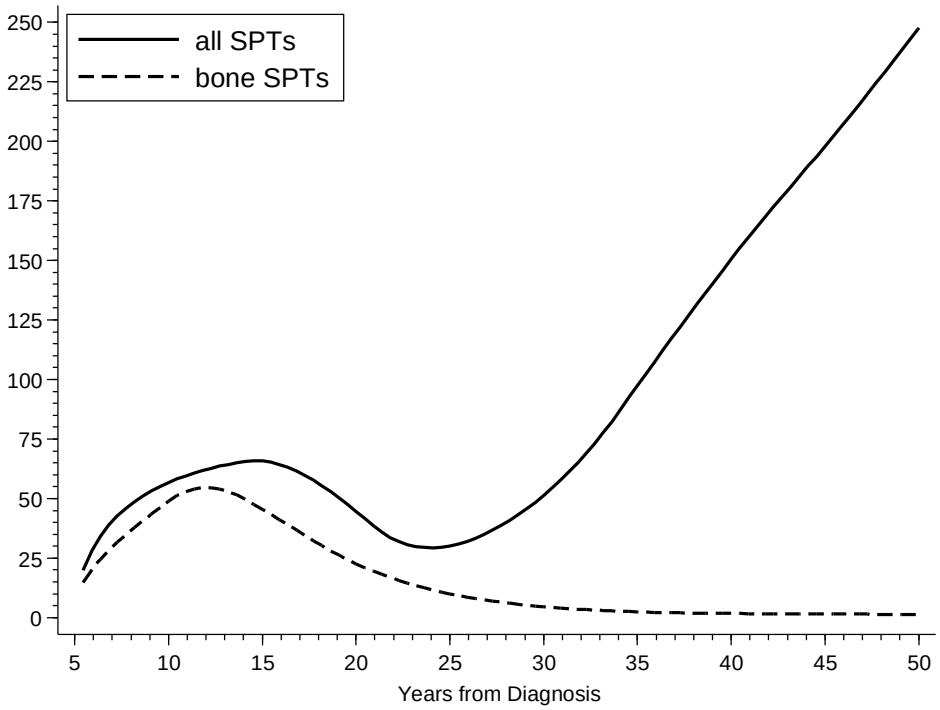


Figure 5.5.3. Absolute excess risk (AER) for all second primary cancers and bone second primary cancers by years from retinoblastoma diagnosis

6 DISCUSSION

This chapter will provide a summary of the key findings from each of the four studies presented in Chapters 2–5, discuss the recommendations for future research, discuss the implications of how our findings may add to current guidelines for clinical follow-up and a final conclusion.

6.1 Summary of Key Findings

In **Chapter 2** we studied the risk of various adverse health and social outcomes among survivors of Wilms' tumour. This was the first ever study to investigate adverse health and social outcomes up to 50 years after diagnosis of Wilms' tumour. Over 65% of survivors survived at least 30 years from childhood cancer diagnosis. Our findings indicated, for the first time, that survivors experienced a substantial increase in premature mortality after 30 years from childhood cancer diagnosis—75% of the excess deaths during this period were attributable to SPNs (50%) and cardiac diseases (25%). The number of excess cases of SPN occurring after 30 years from childhood cancer diagnosis was mainly attributable to digestive (41%) and breast (7%) cancer. Although their perception of their general health was significantly lower than expected from the general population, Wilms' tumour survivors appear to have a healthier lifestyle (being less likely than expected to be a smoker and consuming lower than expected amounts of alcohol) than expected from the general population. They experienced limited physical functioning in everyday tasks, female Wilms' tumour survivors were more likely to give birth prematurely and more underweight offspring and male Wilms' tumour survivors were significantly less likely to be married than expected from the general population.

In **Chapter 3** we investigated the risks of hospitalisation due to specific renal diseases subsequent to five-year survival after childhood cancer diagnosis. Overall, survivors of childhood cancer were twice as likely of being hospitalised due to renal disease than expected from the general population. Survivors of neuroblastoma, Wilms' tumour and soft tissue sarcoma were at highest multiplicative excess risk of being hospitalized for renal disease with 4-fold, 3-fold and 3-fold the risk expected from the general population, respectively. After adjusting for confounders, survivors aged up to 29 had a significantly elevated risk of hospitalisation for renal disease—the risk decreased after 30 years of age. Childhood cancer survivors had a significantly elevated risk of being hospitalised for each specific renal disease which we investigated (glomerular disease, renal tubulo-interstitial disease, renal failure, urolithiasis, urinary tract infection, other kidney disease and other urinary system disease). The excess risk of chronic renal failure was greatest among survivors of Wilms' tumour who had 30-times the expected risk of being hospitalised compared to the general population. Wilms' tumour survivors had a 15-fold expected risk of hospitalisation due to acute renal failure, which has not been reported previously. The multiplicative excess risk of hospitalistion significantly decreased, all specific renal diseases, with increasing attained age.

In **Chapter 4** we describe the risks of developing SPNs in specific digestive sites using a large pan-European cohort of childhood cancer survivors. Overall, childhood cancer survivors in Europe were four times more likely to develop a SPN in the digestive system than expected from the general population. After adjusting for other risk factors, the risk significantly decreased with attained age and females were less likely to develop a digestive SPN compared to males. Heterogeneity was observed

between countries but this was not unexpected as survivors residing in different countries were likely to be subject to different treatment regimens and some cohorts were hospital-based. This was the first ever study to investigate the development of SPNs in specific sites of the digestive system by specific types of childhood cancer diagnosis as no previous study had sufficient numbers to do so. Survivors of Wilms' tumour experienced the highest excess risk of digestive cancer 15-fold expected, and Wilms' survivors experienced 56-fold, 24-fold, 11-fold and 9-fold the expected risk of liver, pancreatic, stomach and colorectal cancer, respectively. Survivors of Hodgkin's lymphoma experienced the second highest excess risk of digestive cancers 9-fold expected, and Hodgkin's survivors experienced an 8-fold, 7-fold, 6-fold and 6-fold expected risk of colorectal, liver, stomach and pancreatic cancer, respectively.

In **Chapter 5** we studied the risk of various adverse health and social outcomes among survivors of heritable retinoblastoma. This study investigated adverse health and social outcomes beyond 50 years of follow up in heritable retinoblastoma survivors, as over 90% of these survivors survived at least 25 years from childhood cancer diagnosis. This was the first ever population-based study to investigate premature mortality and risk of SPNs by specific modes of radiotherapy treatment. Overall, survivors were 18-times more likely to die from a SPN compared to the general population. This risk significantly increased to 33-fold for survivors who received external beam radiotherapy; the risk among survivors who had received either brachytherapy and or no radiotherapy were not significantly different. The excess risk of premature death due to SPNs remained substantially elevated throughout the entire period of follow-up. In the first 25-year period following childhood cancer diagnosis, survivors were 356-times more likely than expected to

develop a bone SPN and in the period 25-50 years after childhood cancer diagnosis, survivors were significantly more likely to develop a soft tissue, digestive, genitourinary and breast SPN. The risk of SPN developing above the shoulder was 4-fold higher among those who received external beam radiotherapy than among those not irradiated. Survivors of heritable retinoblastoma had a 6-fold risk of becoming blind, 17-fold risk of developing cataracts and 28-fold risk of detached retina compared to survivors of all other cancers. Despite these adverse outcomes, heritable retinoblastoma survivors lead a healthier lifestyle by smoking less and drinking less alcohol than expected from the general population and achieve better educational qualifications than expected from the general population. These findings are important in informing not only clinicians and health providers, but also survivors themselves.

6.2 Recommendations for Future Research and Evidence Based Clinical Follow-up Guidelines

The four studies that we have presented in this thesis relate to survivors who were treated with radiotherapy and chemotherapy many decades ago of which a large proportion had received radiotherapy and chemotherapy as part of their initial treatment. The treatment regimens have changed over recent decades but the majority of current survivors, at least 30 years from diagnosis, received radiotherapy and chemotherapy and the risks presented in this thesis relates directly to them. The major strength of this thesis was that the four studies used population-based data and was not subject to selection-bias. Because the BCCSS is the largest population-based study of childhood cancer survivors in the world, a large proportion of

survivors were also on long-term follow-up that allowed us to investigate the risks of late effects up to 50 years after diagnosis (which previous studies were not able to do). However, the lack of detailed treatment information limited us from investigating the risks of such late effects by doses of radiotherapy or specific types of chemotherapeutic drugs. The establishment of a national clinical cohort – which is currently being set up, will hopefully address the issue of the lack of detailed treatment information.

The studies in **Chapter 3** and **Chapter 4** will be discussed first as there is little research currently available in the public domain. The studies in **Chapter 2** and **Chapter 5** will be discussed afterwards relating to current clinical follow-up guidelines.

The study in **Chapter 3** was the first to investigate risks of hospitalisations due to specific renal diseases after five-year survival by type of childhood cancer diagnosis. Thus it was not possible to make comparisons of our findings to other studies. Therefore the risk estimates produced should be useful to those producing and updating evidence based clinical follow-up guidelines relating to renal outcomes. The establishment of a clinical cohort would allow absolute risks to be related to more detailed stratification in terms of treatment.

The study in **Chapter 4** was the first to investigate risks of specific digestive SPNs after five-year survival of childhood cancer by type of childhood cancer diagnosis. The large-scale pan-European cohort of childhood cancer survivors allowed us to

observe digestive SPNs and specific digestive SPNs (such as colorectal, liver, stomach, pancreas). We could only make comparisons to one other study, which investigated the risk of specific digestive SPN similar to our study. However, no studies had sufficient numbers to investigate specific digestive SPN by type of childhood cancer diagnosis. Therefore the risk estimates produced should again be useful to those producing and updating evidence based clinical follow-up guidelines.

The study in **Chapter 2** demonstrated that survivors of Wilms' tumour are at increased risk of adverse health and social outcomes. In particular, this study describes the causes of premature mortality and the risks of SPNs after 30 years from Wilms' tumour diagnosis for the first time. Although there are recommendations, there is currently no formal guideline relating to long-term clinical follow-up for survivors of Wilms' tumour. Two sources recommend frequent follow-up visits and screening for recurrence of the tumour and also heart function tests if survivors were treated with anthracyclines[227,228].

This thesis reports the substantial increase in mortality after 30 years from Wilms' tumour diagnosis—75% of the excess risk after 30 years from diagnosis was attributable to SPN (50%) and cardiac disease (25%). Wilms' tumour survivors experienced a 5-fold risk of developing SPNs compared to the general population. Digestive SPN was most prevalent after 30 years from Wilms' tumour diagnosis and had the highest risk during this period (18-fold) compared to the general population. All Wilms' tumour survivors who developed a digestive SPN had received abdominal radiotherapy and those who developed breast SPN had received abdominal or chest radiotherapy. Survivors were leading a healthier lifestyle by being 30% less likely to

smoke and consume alcohol. Female survivors of Wilms' tumour had a 3-fold risk of giving birth prematurely and low birth weight compared to the general population.

(1) After 30 years from initial diagnosis, follow-up should focus on surveillance relating to SPNs and cardiac diseases, as 75% of excess deaths during this period were attributable to these causes of death in survivors of Wilms' tumour.

(2) Among those receiving direct abdominopelvic radiotherapy, the absolute risk of bowel cancer exceeds that of individuals with two first degree relatives with bowel cancer and the option of colonoscopy needs to be considered.

(3) The increased risk of low birth weight and premature births among female survivors of Wilms' tumour who received direct abdominopelvic irradiation, which is well established, means that such pregnancies should receive closer monitoring than normal pregnancies.

The study in **Chapter 5** demonstrated that survivors of heritable retinoblastoma are at increased risk of adverse health and social outcomes. In particular, this study describes the risks of premature mortality and the risks of SPNs by treatment modality up beyond 50 years of from initial childhood cancer diagnosis. A current guideline recommends frequent active monitoring after 5-year survival (up to 9 years of age) for survivors of retinoblastoma, particularly those who test positive for the RB1 gene or has a family history of retinoblastoma[229]. This guideline, along with the COG guideline, recommends evaluation of the eyes for radiation-related medical conditions such as cataracts, detached retina and other vision problems during

follow-up visits[229,230]. Currently, follow-up examinations focus on screening for SPNs, genetic counselling and evaluation of eye-related medical conditions[229,231].

This thesis reports the excess risks of premature mortality extending beyond 50 years of follow-up, a 4-fold increased risk of SPNs developing above the shoulder if survivors received external beam radiotherapy, significantly increased risk of specific eye-related medical conditions (such as blindness, cataracts and detached retina).

(1) Monitoring of SPNs above the shoulder is recommended for survivors who received external beam radiotherapy.

(2) Surveillance and survivor self-awareness in relation to bone tumours is recommended for survivors who have not yet accrued 25 years of follow-up from diagnosis and similarly for soft tissue sarcoma, digestive, genitourinary and breast carcinoma in those who have been on follow-up for more than 25 years of follow-up since diagnosis.

6.3 Conclusion

This thesis aimed to contribute knowledge relating to the risks of adverse outcomes following survival after childhood cancer. The four studies included in this thesis describe a variety of adverse health and social outcomes and found that (i) survivors of Wilms' tumour are at substantially increased excess risk of premature mortality after 30 years from first diagnosis, compared to that expected from the general population, which were mainly due to SPNs and cardiac disease; (ii) childhood

cancer survivors had a significantly increased risk of being hospitalised for each specific renal disease which we investigated (glomerular disease, renal tubulo-interstitial disease, renal failure, urolithiasis, urinary tract infection, other kidney disease and other urinary system disease); (iii) childhood cancer survivors in Europe were four times as likely to develop a SPN in the digestive system compared to the general population; and (iv) survivors of heritable retinoblastoma who received external beam radiotherapy was four times more likely to develop a SPN above the shoulder compared to those who did not receive any radiotherapy.

The new findings from the studies presented in this thesis contribute to the existing literature relating to the risks of adverse health and social outcomes among childhood cancer survivors and provide unbiased and reliable evidence to help risk stratification of survivors, help updating evidence based clinical follow-up guidelines and the evaluation of proposed future treatment protocols from and risk and benefit perspective.

7 REFERENCES

1. Stiller C: National Registry of Childhood Tumours Progress Report, 2012, pp http://www.ncin.org.uk/publications/reports/

2. Cancer Research UK: Children's cancers survival statistics, 2016, pp http://www.cancerresearchuk.org/health-professional/cancer-statistics/childrens-cancers/survival#heading-Zero

3. Ward E, DeSantis C, Robbins A, et al: Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin 64:83-103, 2014

4. Gatta G, Botta L, Rossi S, et al: Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5--a population-based study. Lancet Oncol 15:35-47, 2014

5. Stiller CA, Kroll ME, Pritchard-Jones K: Population survival from childhood cancer in Britain during 1978-2005 by eras of entry to clinical trials. Ann Oncol 23:2464-9, 2012

6. Armstrong GT, Stovall M, Robison LL: Long-Term Effects of Radiation Exposure among Adult Survivors of Childhood Cancer: Results from the Childhood Cancer Survivor Study. Radiation Research 174:840-850, 2010

7. Hudson MM, Ness KK, Gurney JG, et al: Clinical ascertainment of health outcomes among adults treated for childhood cancer. JAMA 309:2371-81, 2013

8. Reulen RC, Winter DL, Frobisher C, et al: Long-term cause-specific mortality among survivors of childhood cancer. JAMA 304:172-9, 2010

9. Rose SR, Horne VE, Howell J, et al: Late endocrine effects of childhood cancer. Nat Rev Endocrinol, 2016

10. Steliarova-Foucher E, Stiller C, Lacour B, et al: International Classification of Childhood Cancer, third edition. Cancer 103:1457-67, 2005

11. Children With Cancer: Wilms' Tumour Incidence, 2015, pp http://www.childrenwithcancer.org.uk/wilms-tumour

12. Carli M, Frascella E, Tournade MF, et al: Second malignant neoplasms in patients treated on SIOP Wilms tumour studies and trials 1, 2, 5, and 6. Med Pediatr Oncol 29:239-44, 1997

13. Macmillan Cancer Support: Wilms' Tumour in Children, 2015, pp http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Childrenscancers/Typesofchildrenscancers/Wilmstumour.aspx#DynamicJumpMenuManager_6_Anchor_3

14. Treatment by type and stage of Wilms' tumour, 2016, pp http://www.cancer.org/cancer/wilmstumor/detailedguide/wilms-tumor-treating-by-stage

15. Macmillan: Types of treatment for Wilms' tumour, 2016, pp http://www.macmillan.org.uk/Cancerinformation/Cancertypes/Childrenscancers/Typesofchildrenscancers/Wilmstumour.aspx#DynamicJumpMenuManager_6_Anchor_7

16. Children with Cancer: Wilms' tumour, 2016, pp http://www.childrenwithcancer.org.uk/wilms-tumour

17. Chemotherapy for Wilms' tumour, 2016, pp http://www.cancer.org/cancer/wilmstumor/detailedguide/wilms-tumor-treating-chemotherapy

18. John Hopkin's Medicine: Wilms' Tumour, 2016, pp http://www.hopkinsmedicine.org/kimmel_cancer_center/centers/pediatric_oncology/cancer_types/wilms_tumor.html

19. Irtan S, Jitlal M, Bate J, et al: Risk factors for local recurrence in Wilms tumour and the potential influence of biopsy - the United Kingdom experience. Eur J Cancer 51:225-32, 2015

20. Mills MB, Hudgins L, Balise RR, et al: Mutation risk associated with paternal and maternal age in a cohort of retinoblastoma survivors. Hum Genet 131:1115-22, 2012

21. NCI: Retinoblastoma Treatment (PDQ®), 2015, pp http://www.cancer.gov/types/retinoblastoma/patient/retinoblastoma-treatment-pdq

22. Patient Info: Retinoblastoma - what is retinoblastoma and retinal tumours, 2015, pp http://patient.info/doctor/retinoblastoma-pro

23. Broaddus E, Topham A, Singh AD: Survival with retinoblastoma in the USA: 1975-2004. Br J Ophthalmol 93:24-7, 2009

24. MacCarthy A, Draper GJ, Steliarova-Foucher E, et al: Retinoblastoma incidence and survival in European children (1978-1997). Report from the Automated Childhood Cancer Information System project. Eur J Cancer 42:2092-102, 2006

25. Kaiser PK, Scott IU, O'Brien JM, et al: Retinoblastoma. Digital Journal of Opthalmology, 2003

26. Radiation therapy for retinoblastoma, 2016, pp http://www.cancer.org/cancer/retinoblastoma/detailedguide/retinoblastoma-treating-radiation-therapy

27. How is retinoblastoma treated?, 2016, pp http://www.cancer.org/cancer/retinoblastoma/detailedguide/retinoblastoma-treating-general-info

28. Laser therapy (photocoagulation) for retinoblastoma, 2016, pp http://www.cancer.org/cancer/retinoblastoma/detailedguide/retinoblastoma-treating-laser-therapy

29. Cryotherapy for retinoblastoma, 2016, pp http://www.cancer.org/cancer/retinoblastoma/detailedguide/retinoblastoma-treating-cryotherapy

30. Children with Cancer UK: About Childhood Cancer: Facts and Figures, 2015, pp http://www.childrenwithcancer.org.uk/facts-and-figures

31. Robertson CM, Hawkins MM, Kingston JE: Late deaths and survival after childhood cancer: implications for cure. BMJ 309:162-6, 1994

32. Moller TR, Garwicz S, Barlow L, et al: Decreasing late mortality among five-year survivors of cancer in childhood and adolescence: a population-based study in the Nordic countries. J Clin Oncol 19:3173-81, 2001

33. Mertens AC: Cause of mortality in 5-year survivors of childhood cancer. Pediatr Blood Cancer 48:723-6, 2007

34. Mertens AC, Liu Q, Neglia JP, et al: Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst 100:1368-79, 2008

35. Cardous-Ubbink MC, Heinen RC, Langeveld NE, et al: Long-term cause-specific mortality among five-year survivors of childhood cancer. Pediatr Blood Cancer 42:563-73, 2004

36. Dama E, Pastore G, Mosso ML, et al: Late deaths among five-year survivors of childhood cancer. A population-based study in Piedmont Region, Italy. Haematologica 91:1084-91, 2006

37. Hawkins MM, Kingston JE, Kinnier Wilson LM: Late deaths after treatment for childhood cancer. Arch Dis Child 65:1356-63, 1990

38. Reulen RC, Frobisher C, Winter DL, et al: Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. JAMA 305:2311-9, 2011

39. Bassal M: Risk of Selected Subsequent Carcinomas in Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study. Journal of Clinical Oncology 24:476-483, 2006

40. Henderson TO, Whitton J, Stovall M, et al: Secondary sarcomas in childhood cancer survivors: a report from the Childhood Cancer Survivor Study. J Natl Cancer Inst 99:300-8, 2007

41. Davies SM: Subsequent malignant neoplasms in survivors of childhood cancer: Childhood Cancer Survivor Study (CCSS) studies. Pediatr Blood Cancer 48:727-30, 2007

42. Robison LL: Treatment-associated subsequent neoplasms among long-term survivors of childhood cancer: the experience of the Childhood Cancer Survivor Study. Pediatr Radiol 39 Suppl 1:S32-7, 2009

43. Meadows AT, Friedman DL, Neglia JP, et al: Second neoplasms in survivors of childhood cancer: findings from the Childhood Cancer Survivor Study cohort. J Clin Oncol 27:2356-62, 2009

44. Friedman DL, Whitton J, Leisenring W, et al: Subsequent neoplasms in 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst 102:1083-95, 2010

45. Armstrong GT, Liu W, Leisenring W, et al: Occurrence of Multiple Subsequent Neoplasms in Long-Term Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study. Journal of Clinical Oncology 29:3056-3064, 2011

46. Reulen RC, Zeegers MP, Wallace WH, et al: Pregnancy outcomes among adult survivors of childhood cancer in the British Childhood Cancer Survivor Study. Cancer Epidemiol Biomarkers Prev 18:2239-47, 2009

47. Green DM, Lange JM, Peabody EM, et al: Pregnancy outcome after treatment for Wilms tumor: a report from the national Wilms tumor long-term follow-up study. J Clin Oncol 28:2824-30, 2010

48. Green DM, Whitton JA, Stovall M, et al: Pregnancy outcome of female survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Am J Obstet Gynecol 187:1070-80, 2002

49. Green DM: Pregnancy Outcome of Partners of Male Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study. Journal of Clinical Oncology 21:716-721, 2003

50. Signorello LB, Cohen SS, Bosetti C, et al: Female survivors of childhood cancer: preterm birth and low birth weight among their children. J Natl Cancer Inst 98:1453-61, 2006

51. Lancashire ER, Frobisher C, Reulen RC, et al: Educational attainment among adult survivors of childhood cancer in Great Britain: a population-based cohort study. J Natl Cancer Inst 102:254-70, 2010

52. Boman KK, Lindblad F, Hjern A: Long-term outcomes of childhood cancer survivors in Sweden: a population-based study of education, employment, and income. Cancer 116:1385-91, 2010

53. Gerhardt CA, Dixon M, Miller K, et al: Educational and occupational outcomes among survivors of childhood cancer during the transition to emerging adulthood. J Dev Behav Pediatr 28:448-55, 2007

54. Reulen RC, Winter DL, Lancashire ER, et al: Health-status of adult survivors of childhood cancer: a large-scale population-based study from the British Childhood Cancer Survivor Study. Int J Cancer 121:633-40, 2007

55. Essig S, von der Weid NX, Strippoli MP, et al: Health-related quality of life in long-term survivors of relapsed childhood acute lymphoblastic leukemia. PLoS One 7:e38015, 2012

56. Sundberg KK, Wettergren L, Frisk P, et al: Self-reported quality of life in long-term survivors of childhood lymphoblastic malignancy treated with hematopoietic stem cell transplantation versus conventional therapy. Pediatr Blood Cancer 60:1382-7, 2013

57. Frobisher C, Lancashire ER, Winter DL, et al: Long-term population-based marriage rates among adult survivors of childhood cancer in Britain. Int J Cancer 121:846-55, 2007

58. Frobisher C, Lancashire ER, Winter DL, et al: Long-term population-based divorce rates among adult survivors of childhood cancer in Britain. Pediatr Blood Cancer 54:116-22, 2010

59. Wengenroth L, Rueegg CS, Michel G, et al: Life partnerships in childhood cancer survivors, their siblings, and the general population. Pediatr Blood Cancer 61:538-45, 2014

60. Koch SV, Kejs AM, Engholm G, et al: Marriage and divorce among childhood cancer survivors. J Pediatr Hematol Oncol 33:500-5, 2011

61. Frobisher C, Winter DL, Lancashire ER, et al: Extent of smoking and age at initiation of smoking among adult survivors of childhood cancer in Britain. J Natl Cancer Inst 100:1068-81, 2008

62. Gandini S, Botteri E, Iodice S, et al: Tobacco smoking and cancer: a meta-analysis. Int J Cancer 122:155-64, 2008

63. Carswell K, Chen Y, Nair RC, et al: Smoking and binge drinking among Canadian survivors of childhood and adolescent cancers: a comparative, population-based study. Pediatr Blood Cancer 51:280-7, 2008

64. Frobisher C, Lancashire ER, Reulen RC, et al: Extent of alcohol consumption among adult survivors of childhood cancer: the British Childhood Cancer Survivor Study. Cancer Epidemiol Biomarkers Prev 19:1174-84, 2010

65. Clarke SA, Eiser C: Health behaviours in childhood cancer survivors: a systematic review. Eur J Cancer 43:1373-84, 2007

66. Lown EA, Goldsby R, Mertens AC, et al: Alcohol consumption patterns and risk factors among childhood cancer survivors compared to siblings and general population peers. Addiction 103:1139-48, 2008

67. Armstrong GT, Ross JD: Late Cardiotoxicity in Aging Adult Survivors of Childhood Cancer. Prog Pediatr Cardiol 36:19-26, 2014

68. Franco VI, Henkel JM, Miller TL, et al: Cardiovascular effects in childhood cancer survivors treated with anthracyclines. Cardiol Res Pract 2011:134679, 2011

69. Dekkers IA, Blijdorp K, Cransberg K, et al: Long-term nephrotoxicity in adult survivors of childhood cancer. Clin J Am Soc Nephrol 8:922-9, 2013

70. Knijnenburg SL, Jaspers MW, van der Pal HJ, et al: Renal dysfunction and elevated blood pressure in long-term childhood cancer survivors. Clin J Am Soc Nephrol 7:1416-27, 2012

71. Jones DP, Spunt SL, Green D, et al: Renal late effects in patients treated for cancer in childhood: a report from the Children's Oncology Group. Pediatr Blood Cancer 51:724-31, 2008

72. Cardous-Ubbink MC, Heinen RC, Bakker PJ, et al: Risk of second malignancies in long-term survivors of childhood cancer. Eur J Cancer 43:351-62, 2007

73. Neglia JP, Friedman DL, Yasui Y, et al: Second malignant neoplasms in five-year survivors of childhood cancer: childhood cancer survivor study. J Natl Cancer Inst 93:618-29, 2001

74. Olsen JH, Garwicz S, Hertz H, et al: Second malignant neoplasms after cancer in childhood or adolescence. Nordic Society of Paediatric Haematology and Oncology Association of the Nordic Cancer Registries. BMJ 307:1030-6, 1993

75. World Cancer Research Fund International: Worldwide data, 2016, pp http://www.wcrf.org/int/cancer-facts-figures/worldwide-data

76. Cancer Research UK: Bowel Cancer Incidence Statistics, 2015, pp http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/incidence#heading-Zero

77. Cancer Research UK: Bowel Cancer Survival Statistics, 2016, pp http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/survival#heading-Zero

78. Tukenova M, Diallo I, Anderson H, et al: Second malignant neoplasms in digestive organs after childhood cancer: a cohort-nested case-control study. Int J Radiat Oncol Biol Phys 82:e383-90, 2012

79. Henderson TO, Oeffinger KC, Whitton J, et al: Secondary gastrointestinal cancer in childhood cancer survivors: a cohort study. Ann Intern Med 156:757-66, W-260, 2012

80. Cancer Research UK: Liver Cancer Incidence Statistics, 2016, pp http://www.cancerresearchuk.org/content/liver-cancer-incidence-statistics#heading-Zero

81. Survival Rates for Liver Cancer, 2016, pp http://www.cancer.org/cancer/livercancer/detailedguide/liver-cancer-survival-rates

82. Cancer Research UK: Stomach Cancer Incidence Statistics, 2016, pp http://www.cancerresearchuk.org/content/stomach-cancer-incidence-statistics#heading-Zero

83. Cancer Research UK: Stomach Cancer Survival Statistics, 2016, pp http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/stomach-cancer/survival#heading-Zero

84. Cancer Research UK: Pancreatic Cancer Incidence Statistics, 2016, pp http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/pancreatic-cancer/incidence#heading-Zero

85. Cancer Research UK: Pancreatic Cancer Survival Statistics, 2016, pp http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/pancreatic-cancer/survival#heading-Zero

86. Oeffinger KC, Mertens AC, Sklar CA, et al: Chronic health conditions in adult survivors of childhood cancer. N Engl J Med 355:1572-82, 2006

87. British Heart Foundation: Cancer and Heart Failure, 2016, pp https://www.bhf.org.uk/research/what-we-research/heart-failure/cancer-and-heart-failure

88. Mulrooney DA, Yeazel MW, Kawashima T, et al: Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. BMJ 339:b4606, 2009

89. van der Pal HJ, van Dalen EC, van Delden E, et al: High risk of symptomatic cardiac events in childhood cancer survivors. J Clin Oncol 30:1429-37, 2012

90. Harake D, Franco VI, Henkel JM, et al: Cardiotoxicity in childhood cancer survivors: strategies for prevention and management. Future Cardiol 8:647-70, 2012

91. Feijen EA, Leisenring WM, Stratton KL, et al: Equivalence Ratio for Daunorubicin to Doxorubicin in Relation to Late Heart Failure in Survivors of Childhood Cancer. J Clin Oncol 33:3774-80, 2015

92. Kremer LC, Caron HN: Anthracycline cardiotoxicity in children. N Engl J Med 351:120-1, 2004

93. van Dalen EC, Caron HN, Kremer LC: Prevention of anthracycline-induced cardiotoxicity in children: the evidence. Eur J Cancer 43:1134-40, 2007

94. NICE: Early identification and management of chronic kidney disease in adults, 2012, pp https://www.nice.org.uk/guidance/cmg37/chapter/322-epidemiological-data

95. NHS: Kidney Disease Key Facts, 2012, pp www.healthcheck.nhs.uk/document.php?o=81

96. Skinner R: Nephrotoxicity of cancer treatment in children. Pediatr Health 4:519-539, 2010

97. Diller L, Chow EJ, Gurney JG, et al: Chronic disease in the Childhood Cancer Survivor Study cohort: a review of published findings. J Clin Oncol 27:2339-55, 2009

98. Wallace WHB, Green DM: Late Effects of Childhood Cancer. Oxford University Press Inc, Arnold, 2004

99. NHS: Chronic Kidney Disease - Causes, 2015, pp http://www.nhs.uk/conditions/kidney-disease-chronic/pages/causes.aspx

100. Skinner R, Sharkey IM, Pearson AD, et al: Ifosfamide, mesna, and nephrotoxicity in children. J Clin Oncol 11:173-90, 1993

101. Brock PR, Koliouskas DE, Barratt TM, et al: Partial reversibility of cisplatin nephrotoxicity in children. J Pediatr 118:531-4, 1991

102. Rossi R, Kleta R, Ehrich JH: Renal involvement in children with malignancies. Pediatr Nephrol 13:153-62, 1999

103. Green DM, Nolan VG, Kawashima T, et al: Decreased fertility among female childhood cancer survivors who received 22-27 Gy hypothalamic/pituitary irradiation: a report from the Childhood Cancer Survivor Study. Fertil Steril 95:1922-7, 1927 e1, 2011

104. Antal Z, Sklar CA: Gonadal Function and Fertility Among Survivors of Childhood Cancer. Endocrinol Metab Clin North Am 44:739-49, 2015

105. Vern-Gross TZ, Bradley JA, Rotondo RL, et al: Fertility in childhood cancer survivors following cranial irradiation for primary central nervous system and skull base tumors. Radiother Oncol 117:195-205, 2015

106. Lee SH, Shin CH: Reduced male fertility in childhood cancer survivors. Ann Pediatr Endocrinol Metab 18:168-72, 2013

107. Wasilewski-Masker K, Seidel KD, Leisenring W, et al: Male infertility in long-term survivors of pediatric cancer: a report from the childhood cancer survivor study. J Cancer Surviv 8:437-47, 2014

108. Reinmuth S, Hohmann C, Rendtorff R, et al: Impact of chemotherapy and radiotherapy in childhood on fertility in adulthood: the FeCt-survey of childhood cancer survivors in Germany. J Cancer Res Clin Oncol 139:2071-8, 2013

109. Green DM, Sklar CA, Boice JD, Jr., et al: Ovarian failure and reproductive outcomes after childhood cancer treatment: results from the Childhood Cancer Survivor Study. J Clin Oncol 27:2374-81, 2009

110. Balachandar S, Dunkel IJ, Khakoo Y, et al: Ovarian function in survivors of childhood medulloblastoma: Impact of reduced dose craniospinal irradiation and high-dose chemotherapy with autologous stem cell rescue. Pediatr Blood Cancer, 2014

111. Gnaneswaran S, Deans R, Cohn RJ: Reproductive late effects in female survivors of childhood cancer. Obstet Gynecol Int 2012:564794, 2012

112. Lantinga GM, Simons AH, Kamps WA, et al: Imminent ovarian failure in childhood cancer survivors. Eur J Cancer 42:1415-20, 2006

113. Larsen EC, Muller J, Schmiegelow K, et al: Reduced ovarian function in long-term survivors of radiation- and chemotherapy-treated childhood cancer. J Clin Endocrinol Metab 88:5307-14, 2003

114. Morse H, Elfving M, Lindgren A, et al: Acute onset of ovarian dysfunction in young females after start of cancer treatment. Pediatr Blood Cancer 60:676-81, 2013

115. Teh WT, Stern C, Chander S, et al: The impact of uterine radiation on subsequent fertility and pregnancy outcomes. Biomed Res Int 2014:482968, 2014

116. Gawade PL, Oeffinger KC, Sklar CA, et al: Lifestyle, distress, and pregnancy outcomes in the Childhood Cancer Survivor Study cohort. Am J Obstet Gynecol 212:47 e1-10, 2015

117. Lie Fong S, van den Heuvel-Eibrink MM, Eijkemans MJ, et al: Pregnancy outcome in female childhood cancer survivors. Hum Reprod 25:1206-12, 2010

118. Chiarelli AM, Marrett LD, Darlington GA: Pregnancy outcomes in females after treatment for childhood cancer. Epidemiology 11:161-6, 2000

119. Hawkins MM, Smith RA: Pregnancy outcomes in childhood cancer survivors: probable effects of abdominal irradiation. Int J Cancer 43:399-402, 1989

120. Mueller BA, Chow EJ, Kamineni A, et al: Pregnancy outcomes in female childhood and adolescent cancer survivors: a linked cancer-birth registry analysis. Arch Pediatr Adolesc Med 163:879-86, 2009

121. Apajasalo M, Sintonen H, Siimes MA, et al: Health-related quality of life of adults surviving malignancies in childhood. Eur J Cancer 32A:1354-8, 1996

122. Crom DB, Chathaway DK, Tolley EA, et al: Health status and health-related quality of life in long-term adult survivors of pediatric solid tumors. Int J Cancer Suppl 12:25-31, 1999

123. Langeveld NE, Grootenhuis MA, Voute PA, et al: Quality of life, self-esteem and worries in young adult survivors of childhood cancer. Psychooncology 13:867-81, 2004

124. Maunsell E, Pogany L, Barrera M, et al: Quality of life among long-term adolescent and adult survivors of childhood cancer. J Clin Oncol 24:2527-35, 2006

125. Rueegg CS, Gianinazzi ME, Rischewski J, et al: Health-related quality of life in survivors of childhood cancer: the role of chronic health problems. J Cancer Surviv 7:511-22, 2013

126. Langeveld NE, Ubbink MC, Last BF, et al: Educational achievement, employment and living situation in long-term young adult survivors of childhood cancer in the Netherlands. Psychooncology 12:213-25, 2003

127. Lorenzi M, McMillan AJ, Siegel LS, et al: Educational outcomes among survivors of childhood cancer in British Columbia, Canada: report of the Childhood/Adolescent/Young Adult Cancer Survivors (CAYACS) Program. Cancer 115:2234-45, 2009

128. Dieluweit U, Debatin KM, Grabow D, et al: Educational and vocational achievement among long-term survivors of adolescent cancer in Germany. Pediatr Blood Cancer 56:432-8, 2011

129. Kelaghan J, Myers MH, Mulvihill JJ, et al: Educational achievement of long-term survivors of childhood and adolescent cancer. Med Pediatr Oncol 16:320-6, 1988

130. Mitby PA, Robison LL, Whitton JA, et al: Utilization of special education services and educational attainment among long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Cancer 97:1115-26, 2003

131. Fidler MM, Frobisher C, Guha J, et al: Long-term adverse outcomes in survivors of childhood bone sarcoma: the British Childhood Cancer Survivor Study. Br J Cancer 112:1857-65, 2015

132. Armstrong GT: Long-term survivors of childhood central nervous system malignancies: the experience of the Childhood Cancer Survivor Study. Eur J Paediatr Neurol 14:298-303, 2010

133. Allen NE, Beral V, Casabonne D, et al: Moderate alcohol intake and cancer incidence in women. J Natl Cancer Inst 101:296-305, 2009

134. Bagnardi V, Rota M, Botteri E, et al: Light alcohol drinking and cancer: a meta-analysis. Ann Oncol 24:301-8, 2013

135. Dossus L, Boutron-Ruault MC, Kaaks R, et al: Active and passive cigarette smoking and breast cancer risk: results from the EPIC cohort. Int J Cancer 134:1871-88, 2014

136. Fedirko V, Tramacere I, Bagnardi V, et al: Alcohol drinking and colorectal cancer risk: an overall and dose-response meta-analysis of published studies. Ann Oncol 22:1958-72, 2011

137. Gaudet MM, Gapstur SM, Sun J, et al: Active smoking and breast cancer risk: original cohort data and meta-analysis. J Natl Cancer Inst 105:515-25, 2013

138. Parkin DM: 3. Cancers attributable to consumption of alcohol in the UK in 2010. Br J Cancer 105 Suppl 2:S14-8, 2011

139. Smith-Warner SA, Spiegelman D, Yaun SS, et al: Alcohol and breast cancer in women: a pooled analysis of cohort studies. JAMA 279:535-40, 1998

140. Stickel F, Schuppan D, Hahn EG, et al: Cocarcinogenic effects of alcohol in hepatocarcinogenesis. Gut 51:132-9, 2002

141. Byrne J, Fears TR, Steinhorn SC, et al: Marriage and divorce after childhood and adolescent cancer. JAMA 262:2693-9, 1989

142. Dama E, Maule MM, Mosso ML, et al: Life after childhood cancer: marriage and offspring in adult long-term survivors--a population-based study in the Piedmont region, Italy. Eur J Cancer Prev 18:425-30, 2009

143. Janson C, Leisenring W, Cox C, et al: Predictors of marriage and divorce in adult survivors of childhood cancers: a report from the Childhood Cancer Survivor Study. Cancer Epidemiol Biomarkers Prev 18:2626-35, 2009

144. Rauck AM, Green DM, Yasui Y, et al: Marriage in the survivors of childhood cancer: a preliminary description from the Childhood Cancer Survivor Study. Med Pediatr Oncol 33:60-3, 1999

145. Pivetta E, Maule MM, Pisani P, et al: Marriage and parenthood among childhood cancer survivors: a report from the Italian AIEOP Off-Therapy Registry. Haematologica 96:744-51, 2011

146. Stiller CA: Childhood cancer in Britain: incidence, survival, mortality. Oxford, Oxford University Press, 2007

147. Winther JF, Kenborg L, Byrne J, et al: Childhood cancer survivor cohorts in Europe. Acta Oncol 54:655-68, 2015

148. Termuhlen AM, Tersak JM, Liu Q, et al: Twenty-five year follow-up of childhood Wilms tumor: a report from the Childhood Cancer Survivor Study. Pediatr Blood Cancer 57:1210-6, 2011

149. Breslow NE, Takashima JR, Whitton JA, et al: Second malignant neoplasms following treatment for Wilm's tumor: a report from the National Wilms' Tumor Study Group. J Clin Oncol 13:1851-9, 1995

150. Breslow NE, Lange JM, Friedman DL, et al: Secondary malignant neoplasms after Wilms tumor: an international collaborative study. Int J Cancer 127:657-66, 2010

151. Wright KD, Green DM, Daw NC: Late effects of treatment for wilms tumor. Pediatr Hematol Oncol 26:407-13, 2009

152. Green DM, Kawashima T, Stovall M, et al: Fertility of female survivors of childhood cancer: a report from the childhood cancer survivor study. J Clin Oncol 27:2677-85, 2009

153. Nathan PC, Ness KK, Greenberg ML, et al: Health-related quality of life in adult survivors of childhood Wilms tumor or neuroblastoma: A report from the childhood cancer survivor study. Pediatr Blood Cancer 49:704-15, 2007

154. Hawkins MM, Lancashire ER, Winter DL, et al: The British Childhood Cancer Survivor Study: Objectives, methods, population structure, response rates and initial descriptive information. Pediatr Blood Cancer 50:1018-25, 2008

155. Coviello V, Bogess M: Cumulative incidence estimation in the presence of compting risks. The Stata Journal 4:103-112, 2004

156. Jenkinson C, Coulter A, Wright L: Short form 36 (SF36) health survey questionnaire: normative data for adults of working age. BMJ 306:1437-40, 1993

157. Richards L F, K., Roberts, C., Fletcher, L., Goddard, E.: Living in Britain. No. 31. Results from the 2002 General Household Survey, in Statistics OfN (ed). London, The Stationary Office, 2004

158. Hailpern SM, Visintainer PF: Odds ratios and logistic regression: further examples of their use and interpretation. The Stata Journal 3:213-225, 2003

159. Rebholz CE, Reulen RC, Toogood AA, et al: Health care use of long-term survivors of childhood cancer: the British Childhood Cancer Survivor Study. J Clin Oncol 29:4181-8, 2011

160. Cotton CA, Peterson S, Norkool PA, et al: Early and late mortality after diagnosis of wilms tumor. J Clin Oncol 27:1304-9, 2009

161. Taylor AJ, Winter DL, Pritchard-Jones K, et al: Second primary neoplasms in survivors of Wilms' tumour--a population-based cohort study from the British Childhood Cancer Survivor Study. Int J Cancer 122:2085-93, 2008

162. Cancer Research UK: Screening for people at high risk of bowel cancer, 2015, pp http://www.cancerresearchuk.org/about-cancer/type/bowel-cancer/about/screening/who-is-screened-for-bowel-cancer

163. Cairns SR, Scholefield JH, Steele RJ, et al: Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). Gut 59:666-89, 2010

164. Speechley KN, Barrera M, Shaw AK, et al: Health-related quality of life among child and adolescent survivors of childhood cancer. J Clin Oncol 24:2536-43, 2006

165. Mort S, Salantera S, Matomaki J, et al: Self-reported health-related quality of life of children and adolescent survivors of extracranial childhood malignancies: a Finnish nationwide survey. Qual Life Res 20:787-97, 2011

166. Hudson MM, Mertens AC, Yasui Y, et al: Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. JAMA 290:1583-92, 2003

167. Zeltzer LK, Recklitis C, Buchbinder D, et al: Psychological status in childhood cancer survivors: a report from the Childhood Cancer Survivor Study. J Clin Oncol 27:2396-404, 2009

168. Reulen RC, Zeegers MP, Jenkinson C, et al: The use of the SF-36 questionnaire in adult survivors of childhood cancer: evaluation of data quality, score reliability, and scaling assumptions. Health Qual Life Outcomes 4:77, 2006

169. Madanat-Harjuoja LM, Malila N, Lahteenmaki PM, et al: Preterm delivery among female survivors of childhood, adolescent and young adulthood cancer. Int J Cancer 127:1669-79, 2010

170. Haupt R, Byrne J, Connelly RR, et al: Smoking habits in survivors of childhood and adolescent cancer. Med Pediatr Oncol 20:301-6, 1992

171. Pastore G, Magnani C, Mosso ML, et al: Marriage and offspring in adult long-term survivors of childhood cancer: a study from the childhood cancer registry of the Piedmont region (Italy). Riv Ital Pediatr 28:121-7, 2002

172. Oeffinger KC, Mertens AC, Hudson MM, et al: Health care of young adult survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. Ann Fam Med 2:61-70, 2004

173. Pritchard-Jones K, Moroz V, Vujanic G, et al: Treatment and outcome of Wilms' tumour patients: an analysis of all cases registered in the UKW3 trial. Ann Oncol 23:2457-63, 2012

174. Breslow NE, Day NE: Statistical Methods in Cancer Research; Volume 2 - The Design and Analyses of Cohort Studies, IARC Scientific Publications, 1987

175. Knijnenburg SL MR, Schouten-Van Meeteren AYN, Bökenkamp A, Blufpand H, van Dulmen-den Broeder E, Veening MA, Kremer LCM, Jaspers MWM: Early and late renal adverse effects after potentially nephrotoxic treatment for childhood cancer (Review). The Cochrane Library 2013, 2013

176. Olowu WA, Adelusola KA, Senbanjo IO, et al: Hypertension, erythrocyturia and proteinuria in childhood non-Hodgkin's lymphoma. Nephrology (Carlton) 11:165-70, 2006

177. Green DM: Evaluation of renal function after successful treatment for unilateral, non-syndromic Wilms tumor. Pediatr Blood Cancer 60:1929-35, 2013

178. Bardi E, Olah AV, Bartyik K, et al: Late effects on renal glomerular and tubular function in childhood cancer survivors. Pediatr Blood Cancer 43:668-73, 2004

179. Skinner R, Parry A, Price L, et al: Persistent nephrotoxicity during 10-year follow-up after cisplatin or carboplatin treatment in childhood: relevance of age and dose as risk factors. Eur J Cancer 45:3213-9, 2009

180. International Statistical Classification of Diseases and Related Health Problems - 10th Revision, World Health Organization, 1996 pp. 679-697

181. Skinner R, Parry A, Price L, et al: Glomerular toxicity persists 10 years after ifosfamide treatment in childhood and is not predictable by age or dose. Pediatr Blood Cancer 54:983-9, 2010

182. Pietila S, Ala-Houhala M, Lenko HL, et al: Renal impairment and hypertension in brain tumor patients treated in childhood are mainly associated with cisplatin treatment. Pediatr Blood Cancer 44:363-9, 2005

183. Hoffmeister PA, Storer BE, Baker KS, et al: Nephrolithiasis in pediatric hematopoietic cell transplantation with up to 40 years of follow-up. Pediatr Blood Cancer 61:417-23, 2014

184. NICE: Chronic kidney disease in adults: assessment and management, 2015, pp http://www.nice.org.uk/guidance/cg182/chapter/1-recommendations#frequency-of-monitoring-2

185. Mertens AC, Yasui Y, Neglia JP, et al: Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. J Clin Oncol 19:3163-72, 2001

186. Cancer Research UK: Cancer incidence for common cancers, 2015, pp http://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/common-cancers-compared#heading-Zero

187. Olsen JH, Moller T, Anderson H, et al: Lifelong cancer incidence in 47,697 patients treated for childhood cancer in the Nordic countries. J Natl Cancer Inst 101:806-13, 2009

188. Garwicz S, Anderson H, Olsen JH, et al: Second malignant neoplasms after cancer in childhood and adolescence: a population-based case-control study in the 5 Nordic countries. The Nordic Society for Pediatric Hematology and Oncology. The Association of the Nordic Cancer Registries. Int J Cancer 88:672-8, 2000

189. Magnani C, Terracini B, Cordero Di Montezemolo L, et al: Incidence of second primary malignancies after a malignant tumor in childhood: a population-based survey in Piedmont (Italy). Int J Cancer 67:6-10, 1996

190. Hjorth L, Haupt R, Skinner R, et al: Survivorship after childhood cancer: PanCare: a European Network to promote optimal long-term care. Eur J Cancer 51:1203-11, 2015

191. J F: IARC/IACR Cancer Registry Tools (IARCcrgTools). 2.05 ed. Lyon, France: Descriptive Epidemiology Group, International Agency for Research on Cancer; 2008.,

192. Steliarova-Foucher E, O'Callaghan M, Ferlay J, et al: The European Cancer Observatory: A new data resource. Eur J Cancer 51:1131-43, 2015

193. V Z, M PZ: SLORA: Slovenia and Cancer. Epidemiology and Cancer Registry. Institute of Oncology and Ljublijana., 2015, pp www.slora.si

194. Hamchou M, Matta H, Ionescu G, et al: Colonic adenocarcinoma as a secondary malignancy after treatment of embryonal rhabdomyosarcoma. World J Pediatr 9:80-3, 2013

195. Nottage K, McFarlane J, Krasin MJ, et al: Secondary colorectal carcinoma after childhood cancer. J Clin Oncol 30:2552-8, 2012

196. Lee KJ, Inoue M, Otani T, et al: Gastric cancer screening and subsequent risk of gastric cancer: a large-scale population-based cohort study, with a 13-year follow-up in Japan. Int J Cancer 118:2315-21, 2006

197. Jess T, Simonsen J, Jorgensen KT, et al: Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years. Gastroenterology 143:375-81 e1; quiz e13-4, 2012

198. Hughes LA, van den Brandt PA, Goldbohm RA, et al: Childhood and adolescent energy restriction and subsequent colorectal cancer risk: results from the Netherlands Cohort Study. Int J Epidemiol 39:1333-44, 2010

199. Kleinerman RA, Tucker MA, Tarone RE, et al: Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: an extended follow-up. J Clin Oncol 23:2272-9, 2005

200. Bhatia S, Yasui Y, Robison LL, et al: High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the Late Effects Study Group. J Clin Oncol 21:4386-94, 2003

201. Schaapveld M, Aleman BM, van Eggermond AM, et al: Second Cancer Risk Up to 40 Years after Treatment for Hodgkin's Lymphoma. N Engl J Med 373:2499-511, 2015

202. Swerdlow AJ, Barber JA, Hudson GV, et al: Risk of second malignancy after Hodgkin's disease in a collaborative British cohort: the relation to age at treatment. J Clin Oncol 18:498-509, 2000

203. Swerdlow AJ, Douglas AJ, Hudson GV, et al: Risk of second primary cancers after Hodgkin's disease by type of treatment: analysis of 2846 patients in the British National Lymphoma Investigation. BMJ 304:1137-43, 1992

204. van Leeuwen FE, Klokman WJ, Veer MB, et al: Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young adulthood. J Clin Oncol 18:487-97, 2000

205. MacCarthy A, Bayne AM, Brownbill PA, et al: Second and subsequent tumours among 1927 retinoblastoma patients diagnosed in Britain 1951-2004. Br J Cancer 108:2455-63, 2013

206. Kleinerman RA, Schonfeld SJ, Tucker MA: Sarcomas in hereditary retinoblastoma. Clin Sarcoma Res 2:15, 2012

207. Fletcher O, Easton D, Anderson K, et al: Lifetime risks of common cancers among retinoblastoma survivors. J Natl Cancer Inst 96:357-63, 2004

208. Araki Y, Matsuyama Y, Kobayashi Y, et al: Secondary neoplasms after retinoblastoma treatment: retrospective cohort study of 754 patients in Japan. Jpn J Clin Oncol 41:373-9, 2011

209. Eng C, Li FP, Abramson DH, et al: Mortality from second tumors among long-term survivors of retinoblastoma. J Natl Cancer Inst 85:1121-8, 1993

210. Francis JH, Kleinerman RA, Seddon JM, et al: Increased risk of secondary uterine leiomyosarcoma in hereditary retinoblastoma. Gynecol Oncol 124:254-9, 2012

211. Kleinerman RA, Tarone RE, Abramson DH, et al: Hereditary retinoblastoma and risk of lung cancer. J Natl Cancer Inst 92:2037-9, 2000

212. Kleinerman RA, Tucker MA, Abramson DH, et al: Risk of soft tissue sarcomas by individual subtype in survivors of hereditary retinoblastoma. J Natl Cancer Inst 99:24-31, 2007

213. Kleinerman RA, Yu CL, Little MP, et al: Variation of second cancer risk by family history of retinoblastoma among long-term survivors. J Clin Oncol 30:950-7, 2012

214. Shinohara ET, DeWees T, Perkins SM: Subsequent malignancies and their effect on survival in patients with retinoblastoma. Pediatr Blood Cancer 61:116-9, 2014

215. Yu CL, Tucker MA, Abramson DH, et al: Cause-specific mortality in long-term survivors of retinoblastoma. J Natl Cancer Inst 101:581-91, 2009

216. Kroll ME, Murphy MF, Carpenter LM, et al: Childhood cancer registration in Britain: capture-recapture estimates of completeness of ascertainment. Br J Cancer 104:1227-33, 2011

217. Rodjan F, Graaf P, Brisse HJ, et al: Second cranio-facial malignancies in hereditary retinoblastoma survivors previously treated with radiation therapy: clinic and radiologic characteristics and survival outcomes. Eur J Cancer 49:1939-47, 2013

218. MacCarthy A, Bayne AM, Draper GJ, et al: Non-ocular tumours following retinoblastoma in Great Britain 1951 to 2004. Br J Ophthalmol 93:1159-62, 2009

219. Dommering CJ, Marees T, van der Hout AH, et al: RB1 mutations and second primary malignancies after hereditary retinoblastoma. Fam Cancer 11:225-33, 2012

220. Marees T, van Leeuwen FE, de Boer MR, et al: Cancer mortality in long-term survivors of retinoblastoma. Eur J Cancer 45:3245-53, 2009

221. Chodick G, Kleinerman RA, Stovall M, et al: Risk of cataract extraction among adult retinoblastoma survivors. Arch Ophthalmol 127:1500-4, 2009

222. Choi SY, Kim MS, Yoo S, et al: Long term follow-up results of external beam radiotherapy as primary treatment for retinoblastoma. J Korean Med Sci 25:546-51, 2010

223. Osman IM, Abouzeid H, Balmer A, et al: Modern cataract surgery for radiation-induced cataracts in retinoblastoma. Br J Ophthalmol 95:227-30, 2011

224. Foster MC, Kleinerman RA, Abramson DH, et al: Tobacco use in adult long-term survivors of retinoblastoma. Cancer Epidemiol Biomarkers Prev 15:1464-8, 2006

225. van Dijk J, Imhof SM, Moll AC, et al: Quality of life of adult retinoblastoma survivors in the Netherlands. Health Qual Life Outcomes 5:30, 2007

226. Follow-up after treatment for retinoblastoma, 2016, pp http://www.cancer.ca/en/cancer-information/cancer-type/retinoblastoma/treatment/follow-up/?region=on

227. Follow-up after treatment for Wilms' tumour, 2016, pp http://www.cancer.ca/en/cancer-information/cancer-type/wilms-tumour/treatment/follow-up/?region=nu

228. What happens after treatment for Wilms' tumour?, 2016, pp http://www.cancer.org/cancer/wilmstumor/detailedguide/wilms-tumor-after-follow-up

229. Follow-up after treatment for retinoblastoma, 2016, pp http://www.cancer.ca/en/cancer-information/cancer-type/retinoblastoma/treatment/follow-up/?region=on

230. Children's Oncology Group (COG) Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and Young Adult Cancer, 2013, pp http://www.survivorshipguidelines.org/pdf/LTFUGuidelines_40.pdf

231. SIGN 132: Long term follow up of survivors of childhood cancer, 2013, pp http://www.sign.ac.uk/pdf/sign132.pdf

8 APPENDIX

8.1 Table of childhood cancer types with corresponding ICD-0 codes

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

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	

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

Tables were extracted from Steliarova-Foucher et al. to describe the type of childhood cancers with the corresponding ICD-O codes[10].

8.2 Female Study Questionnaire from the BCCSS

FEMALE VERSION **STRICTLY CONFIDENTIAL**

DEPARTMENT OF PUBLIC HEALTH AND EPIDEMIOLOGY

UNIVERSITY OF BIRMINGHAM

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

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

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

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

PLEASE WRITE CLEARLY.

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

☎ 0800 328 9419 ☎

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

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

8.4 Glossary of Abbreviations in Alphabetical Order

Abbreviation	Definition
95% CI	95% Confidence Interval
AER	Absolute Excess Risk
BCCSS	British Childhood Cancer Survivor Study
CCRG	Childhood Cancer Registry Group
CHF	Congestive Heart Failure
CKD	Chronic Kidney Disease
CNS	Central Nervous System
CT	Chemotherapy
ECO	European Cancer Observatory
FPN	First Primary Neoplasm
GFR	Glomerular Filtration Rate
GHP	General Health Perception
GHS	General Household Survey
GP	General Practitioner
HES	Hospital Episode Statistics
HRb	Heritable Retinoblastoma
HRQL	Health Related Quality of Life
HSCIC	Health and Social Care Information Centre
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
ICD-O	International Classification of Diseases (Oncology)

NHL	Non-Hodgkin’s Lymphoma
NICE	National Institute of Care and Excellence
NRCT	National Registry of Childhood Tumours
O/E	Observed divided by Expected
OHLS	Oxford Healthy Life Survey
ONS	Office for National Statistics
OR	Odds Ratio
PCP	Primary Care Physician/Provider
PCSF	Pan Care Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies (PanCareSurFup)
Rb	Retinoblastoma
RER	Relative Excess Risk
RR	Risk Ratio
RT	Radiotherapy
SF-36	Short Form 36
SHR	Standardised Hospitalisation Ratio
SIOP	Société Internationale d’Oncologie Pédiatrique (International Society of Paediatric Oncology)
SIR	Standardised Incidence Ratio
SMR	Standardised Mortality Ratio
SPN	Subsequent Primary Neoplasm
STS	Soft Tissue Sarcoma

8.5 Statement of Contributions of the Research

The British Childhood Cancer Survivor Study was set up by Professor Mike Hawkins in 1998. David Winter built electronic databases to store the data and also performed the linkage between the British Childhood Cancer Survivor Study and the Hospital Episode Statistics.

Julie Kelly, Joyeeta Guha, Miranda Fidler, Chloe Bright and myself contributed to the extraction of treatment information (radiotherapy and chemotherapy) for the UK component of the PCSF study.

I examined all medical files related to the 552 heritable retinoblastoma survivors in the British Childhood Cancer Survivor Study and extracted information relating to the type of radiotherapy (external beam or plaque) for the analysis presented in **Chapter 5**.

My supervisors Mike Hawkins, Raoul Reulen and Clare Frobisher provided guidance with regards to the study design, analysis and interpretation of the results. In particular, Mike gave me the opportunity to present my research at various international conferences.