LONG-TERM ADVERSE OUTCOMES FOLLOWING FIVE-YEAR SURVIVAL OF CANCER DIAGNOSED BEFORE 40 YEARS AGE

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ABSTRACT

Purpose: Survival from childhood, teenage, and young adult cancer has increased substantially, with approximately 80% now surviving at least five-years. However, curative treatments are often associated with adverse late effects. This thesis investigated the risk of late adverse health and social outcomes following five-year survival of cancer diagnosed before age 40 years using the British Childhood Cancer Survivor Study (BCCSS) and Teenage and Young Adult Cancer Survivor Study (TYACSS).

Material and Methods: The BCCSS is a population-based cohort of 34,489 five-year survivors of childhood (<15 years) cancer diagnosed from 1940-2006 in Great Britain. The TYACSS is a population-based cohort of 200,945 five-year survivors of teenage and young adult (15-39 years) cancer diagnosed from 1971-2006 in England and Wales.

Results: Some survivors were found to have increased risks of premature mortality, subsequent primary neoplasms, hospitalizations, poor quality-of-life, and psychosocial limitations. However, for premature mortality, the number of excess deaths is decreasing among those more recently diagnosed for several causes-of-death.

Conclusions: Survivors of cancer diagnosed before age 40 are at an increased risk of a range of adverse late effects compared to that expected. The findings reported in this thesis will be useful for risk stratification, updating clinical guidelines, and informing survivors and clinicians.

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PAPERS

Published

- Fidler, M M et al. 2015. "Long-Term Adverse Outcomes in Survivors of Childhood Bone Sarcoma: The British Childhood Cancer Survivor Study." *Br J Cancer* 112(12): 1857–65.

Under Review

- "Aspects of mental health dysfunction among survivors of childhood cancer." Submitted May 19, 2015

In Preparation

- "Population-based long-term cause-specific mortality among 34,489 5-year survivors of childhood cancer in Britain." Article manuscript in progress, to be submitted for publication in Summer 2015.
- "Population-based long-term cardiac mortality among 34,489 5-year survivors of childhood cancer in Britain." Article manuscript in progress, to be submitted for publication in Summer 2015.
- "Population-based long-term respiratory mortality among 235,434 5-year survivors of cancer diagnosed before age 40 years." Article manuscript in progress, to be submitted for publication in Summer 2015.

PRESENTATIONS

14th International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer

June 11-13, 2015

Arlington, VA, United States of America

- Poster Presentation: "Population-based long-term respiratory mortality among 235,434 5-year survivors of cancer diagnosed before age 40 years"

National Cancer Intelligence Network: Cancer Outcomes Conference 2015

June 8-10, 2015

Belfast, United Kingdom

- Oral Presentation: "Population-based long-term respiratory mortality among 235,434 5-year survivors of cancer diagnosed before age 40 years"
- Poster Presentation: "Population-based long-term cause-specific mortality among 34,489 5-yea survivors of childhood cancer"
- Poster Presentation: "Population-based long-term cardiac mortality among 34,489 5-year survivors of childhood cancer"
- Poster Presentation: "Long-term cardiac morbidity among 5-year survivors of childhood cancer"

14th PanCare Meeting

October 8-10, 2014

Lucerne, Switzerland

- Oral Presentation: "Long-term cardiac mortality among 5-year survivors of childhood cancer"

College of Medical and Dental Sciences Festival of Graduate Research 2015

March 30, 2015

Birmingham, United Kingdom

- Oral Presentation: "Long-term premature mortality among survivors of childhood cancer: the British Childhood Cancer Survivor Study"

European Symposium on Late Complications after Childhood Cancer

September 15-16, 2014

Edinburgh, Scotland

- Oral Presentation: "Long-term respiratory mortality among 5-year survivors of childhood, teenage, and young adult cancer"
    - Won 'Giulio D'Angio Prize' for best oral presentation
- Poster Presentation: "Long-term cardiac mortality among 5-year survivors of childhood cancer"

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- Poster Presentation: "Long-term outcomes of pediatric bone sarcoma and its treatment using record linkage: a BCCSS study," presented (poster) at the Cancer Outcomes Conference, June 9-10, 2014 Birmingham, England

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May 12-14, 2014

Wroclaw, Poland

- Oral Presentation: "Cohort characteristics and the incidence of subsequent bone cancers in PanCareSurFup,"

13th International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer

June 13-15, 2013

Memphis, TN, United States of America

- Poster Presentation: "Health and social outcomes of pediatric bone sarcoma survivors in the British Childhood Cancer Survivor Study"

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CHAPTER 1

Introduction

Survivorship from childhood, teenage, and young adult cancers has increased since the 1970s due to improved treatment therapies, centralization of treatment, inclusion in clinical trials, and improved supportive care. Currently, approximately 80% of individuals diagnosed with malignancy under the age of 40 years will become five-year survivors. Although the five-year survival rate is encouraging, these individuals continue to face increased risks of long-term adverse health and social outcomes compared to that expected from the general population. Previous literature has shown increased risks of premature mortality, subsequent cancers, chronic health conditions, poor quality-of-life, and a range of adverse psychosocial outcomes. Due to the fact that the number of survivors of childhood, teenage, and young adult cancers is expected to continue to increase with time, it has become ever more important to investigate the risks and causes of these adverse outcomes in order to determine the public health and healthcare implications.

In this thesis I will utilize the British Childhood Cancer Survivor Study and Teenage and Young Adult Cancer Survivor Study, which combined include approximately 235,000 five-year survivors of cancer diagnosed before the age of 40 years, in order to assess a wide range of adverse outcomes. Due to the large study population size, long available follow-up time, and population-based design of these cohorts, the results from the studies included in this thesis provide a reliable and unbiased basis to develop and update evidence-based clinical follow-up guidelines. Additionally, this research will provide new data for risk stratification and planning intervention studies. In doing so, the ultimate goals of this thesis are to contribute to the current understanding of late effects and provide evidence to assist in the prevention and/or control of excess risks of adverse health outcomes among childhood, teenage, and young adult cancer survivors.

CHAPTER 2

Background

The aim of this chapter is to provide a foundation for the research presented in this thesis by summarizing and critically evaluating the existing literature on childhood, teenage and young adult cancers. A particular emphasis will be placed on evaluating the adverse late effects of cancer and its treatment on health, quality-of-life, and a range of psychosocial outcomes. This chapter will also describe the study populations under investigation and present the main aims of the thesis. Thus, this chapter should serve as the conceptual and methodological underpinning for the five subsequent chapters, which each present an individual study, a corresponding in-depth review of evidence, and the relevant methods for the specific research question under investigation.

2.1. Childhood Cancer

2.1.1. Incidence and Survival

Cancer in childhood, which for this thesis is restricted to individuals aged 0 to 14 years, is relatively rare and accounts for approximately 0.5% of all cancers in Great Britain[1]. Approximately 1,400 children in Great Britain are diagnosed with cancer each year[1]. Boys are more likely to develop cancer compared to girls, with a ratio of approximately 6:5; however, this varies by diagnostic group[1]. In general, the childhood cancer diagnostic groups are classified into the following categories using the *International Classification of Childhood Cancers*[2]: leukemias, lymphomas, central nervous system (CNS) tumors, neuroblastoma, retinoblastoma, renal tumors, hepatic tumors, malignant bone tumors, soft tissue sarcomas, germ cell tumors, and other/unspecified cancers. The most frequent diagnostic groups are leukemias, CNS tumors, and lymphomas, which account for over two-thirds of all childhood cancers (Figure 2.1).

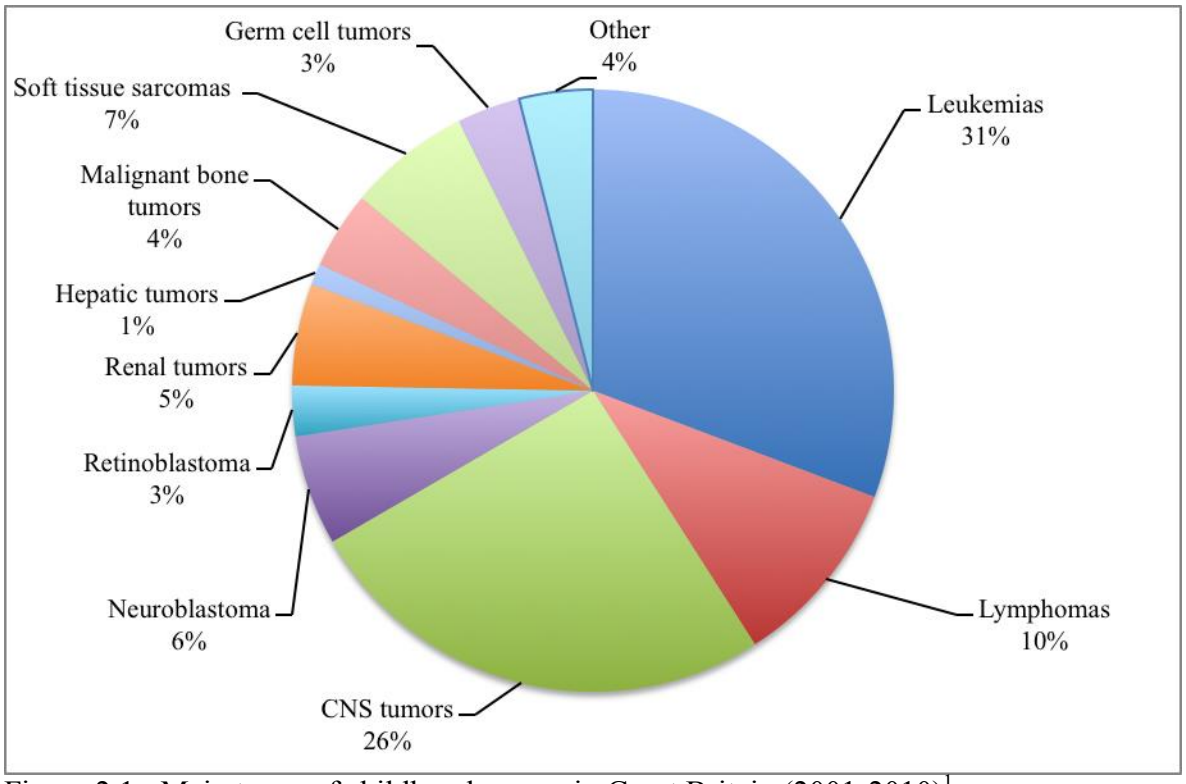

Figure 2.1: Main types of childhood cancer in Great Britain (2001-2010)[1]

Although in Great Britain cancer is the most common cause-of-death among children, accounting for approximately 20% of deaths, survival has improved dramatically over the past several decades (Figure 2.2)[3]. When comparing those diagnosed from 1971-1975 to those diagnosed in 2006-2010, the one-year survival rate increased by 28%, ultimately reaching 91% in the latter group. Similarly, five-year survival after childhood cancer has increased substantially over time; in 1971-1975 only 40% of children diagnosed with cancer survived at least five years, whereas the five-year survival rate for those diagnosed from 2006-2010 was 82%. This pattern of substantial improvements also characterizes ten-year survival, which increased 40% from 1971-1975 to 2001-2005.

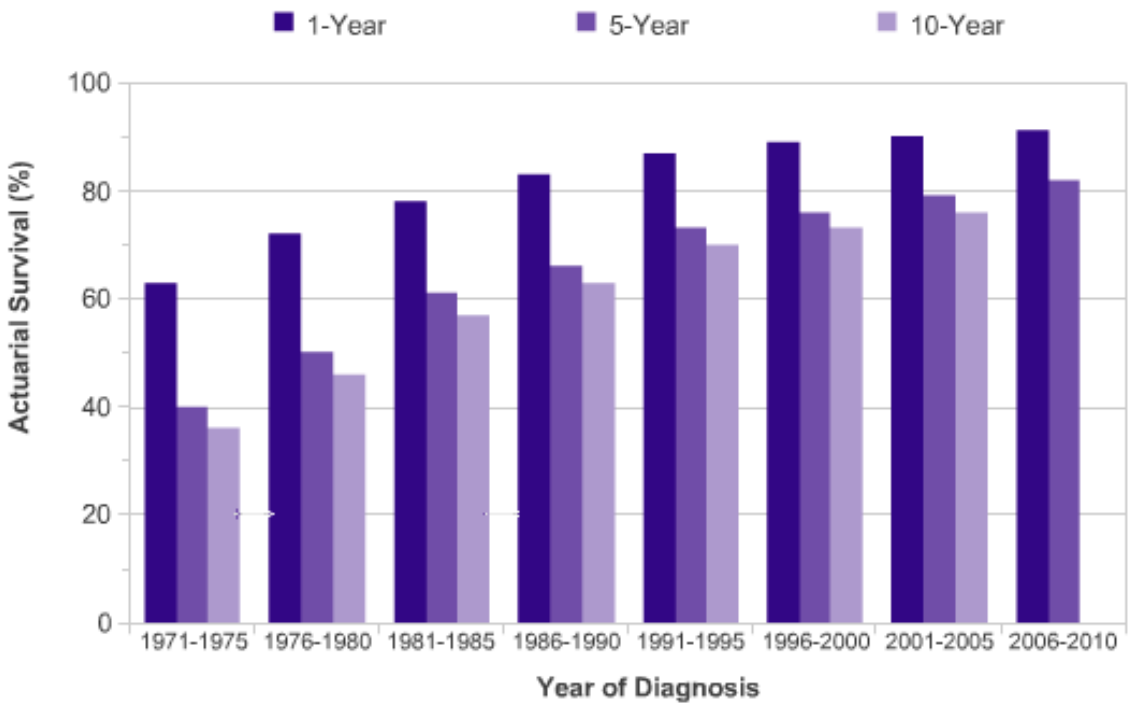

Figure 2.2: One-, five-, and ten-year actuarial survival of childhood cancer in Great Britain (1971-2010)[4]

As a consequence of this improved survival in more recent decades, it has been estimated that there are approximately 33,000 people in the United Kingdom who are alive, previously diagnosed with a childhood cancer, and have survived for at least five years[5]. Each year this survivor population is expected to grow by an additional 1,300 survivors, making it important to not only monitor short-term survival, but also long-term outcomes.

2.1.1. Long-term Follow-Up Guidelines

Various groups have developed recommendations for follow-up of childhood cancer survivors, including the United Kingdom Children's Cancer Study Group[6], Scottish Intercollegiate Guidelines Network[7], United States Children's Oncology Group[8], and Dutch

Childhood Oncology Group[9]. Where possible, the guidelines are developed by using evidence from literature to identify high-risk survivors for a range of outcomes. Unfortunately, evidence may be very weak relating to some outcomes. In general, the guidelines recommend that survivors of childhood cancer should be on active follow-up throughout their lifetime. The recommended model of care is through a long-term follow-up program, although follow-up through a general practitioner or a hybrid of the two is also used[10]. In the early years following diagnosis of the primary cancer, survivors are monitored for recurrences[6,10]; however, as the time since diagnosis increases, the balance changes where survivors are increasingly monitored in order to provide risk-based care for potential late effects of cancer and its treatment[6,10]. The extent of long-term morbidity risk depends on the type and site of the first primary neoplasm, age at treatment, and treatment received[7]. By creating guidelines that stratify recommendations of follow-up based upon these factors, clinicians can anticipate the likely late adverse effects that should be considered, evaluated, and treated for their survivor patients[6]. Furthermore, guidelines also provide educational resources and information on patient counseling[6–9]. Although individual initiatives to develop recommendations for long-term follow-up by countries or regions has led to informative reports, current work is being undertaken through the International Guideline Harmonization Group to establish a universal strategy for childhood cancer survivors[11]. Through this collaborative effort, duplication of efforts will be reduced and the use of expertise would be optimized, ultimately identifying gaps in knowledge in current guidelines[11]. In doing so, this collaborative guideline effort will hopefully reach its ultimate goal of optimizing quality of care and improving quality-of-life for survivors of childhood cancer[11].

2.1.2. Adverse Late Effects

Despite the considerable improvement in survival over time, childhood cancer survivors remain at an increased risk of adverse late effects due to the cancer and its treatment[10,12]. Medical treatments and interventions, such as radiotherapy, chemotherapy, and surgery, utilized to cure or control the cancer and improve survival can have a spectrum of detrimental long-term effects including an increased risk for premature mortality[13–23], second primary neoplasms (SPNs)[21,23–34], cardiac impairments[20,21,23,31–37], endocrine deficiencies[20,21,23,32,34,35,37–41], pulmonary dysfunction[20,23,32,35,42], immune system suppression[21,23,35], gastrointestinal problems[23,32,33], genitourinary disorders[23,32], neurocognitive deficits[20,21,23,32,34,35,43–45], sensory loss[32], musculoskeletal abnormalities[20,23,32,33,35], and infertility[20,23,31,33,35,46–49]. These impairments together with other factors may then cause further limitations with regards to education attainment[50–53], employability[50,54,55], quality-of-life[56–67], and other psychosocial outcomes[33,55,59,68–78]. Thus, as the prevalence of childhood cancer survivors continues to increase, it is ever more important to quantify risks of adverse outcomes and identify potential risk factors in order to provide an evidence base for long-term clinical follow-up and establish opportunities for interventions – both of which aim at reducing the total burden of late effects in existing survivors and those treated for cancer in the future.

2.1.2.1. Premature Mortality

Mortality rates among childhood cancer survivors continue to be elevated far beyond five-year survival when compared to the general population[13–19,79]. Three of the largest studies from Great Britain[13], the United States[14], and the Nordic countries[19] have reported 10.7-, 8.4-, and 8.3-fold increased risks of mortality compared to that expected from the general

population, respectively. The leading cause-of-death in the short-term has been previously shown to be due to recurrence or progression of the childhood cancer[13–16,19,80]. However, as time from original diagnosis increases, the risk of mortality due to SPNs, circulatory diseases, and respiratory causes increases[13–15,19,27,81]; in a study from Great Britain, 77% of the excess number of deaths observed among those surviving beyond 45 years from diagnosis were due to SPNs and circulatory deaths[13]. Although several reports have assessed whether mortality among five-year survivors of childhood cancer differs by treatment era[17–19,82], further assessment is necessary in order to determine the net effect of more modern treatments in both the medium- and long-term. Inevitably, there remains uncertainty as to longer-tem risks in individuals treated more recently in the 1990s and 2000s due to limited follow-up currently.

2.1.2.2. Subsequent Primary Neoplasms

Early reports of cancer-related or treatment-induced SPNs among childhood cancer survivors was published in the 1970s[83]. Since then, the risk of SPNs has been investigated in many cohorts of childhood cancer survivors[24–26,28,29,84]. Within these previous studies, the cumulative risk of a subsequent cancer has been estimated to be between 3-5% at 20-25 years from diagnosis[25,84,85]. However, in a study from Great Britain, the cumulative risk of SPNs in childhood cancer survivors increased to 14% by age 60 years, whilst only 8% was expected[24]. Bone and glioma SPNs accounted for the majority of excess SPNs in survivors aged under 30 years (>50%), whilst breast, respiratory genitourinary, and digestive SPNs increased rapidly with attained age, accounting for 52% of excess SPNs in those aged 40 years or more[24]. Only one large study to date has assessed risk of SPNs by treatment era[84]; in the findings from this Nordic study, the cumulative risk of SPNs at 50 years age was 8.6% in those diagnosed from 1943-1959 (pre-chemotherapy era), 12.2% in those diagnosed from 1960-1974 (first

generation chemotherapy era), and 13.3% in those diagnosed from 1975-2005 (combination chemotherapy era)[84]. The fact that this study found that the cumulative risk for SPNs in fact increased for those treated more recently suggests that this is a crucial question to investigate further. Furthermore, few studies have assessed the risk of SPNs in childhood cancer survivors beyond age 50, and thus reassessment of these risks is necessary with increased follow-up.

2.1.2.3. Chronic Health Conditions

A study of over 10,000 childhood cancer survivors from the United States found that the risk of self-reported chronic health conditions was high[86]. After a mean follow-up of 26.6 years, 62% of survivors reported at least one chronic health condition of a grade 1-4 by the Common Terminology Criteria for Adverse Events (CTCAE) scoring[87], with 27% reporting a condition categorized as severe (grade 3), life-threatening (grade 4), or disabling (grade 4)[86]. A large proportion of these survivors also reported having two (38%) or three or more (24%) chronic conditions of a grade 1-4[86]. These percentages equated to a three-fold increased risk of having at least one chronic condition of a grade 1-4 and a five-fold increased risk of having two or more chronic conditions of a grade 1-4 compared to a sibling comparison group[86]. These findings have been complemented by the results of two other studies that assessed ascertained chronic health conditions among childhood cancer survivors in a hospital clinic setting in the Netherlands[88] and United States[89]. The first of these studies, which assessed 1,362 Dutch survivors, found that 75% of survivors had at least chronic condition of any CTCAE grade, 59% had two or more chronic conditions of any CTCAE grade, and 25% had five or more chronic conditions of any CTCAE grade after a median follow-up period of 17.0 years[88]. Among survivors with chronic conditions, 37% had at least one condition graded a 3

or 4[88]. Similarly, the study from the United States found that, among the 1,713 participants, 98% had one or more chronic health conditions graded 1-4 according to the CTCAE, with 68% of survivors having a severe, life-threatening, or disabling condition[89]. Over time, the incidence of chronic conditions has been reported to increase with no suggestion of a plateau[86,89,90]; however, this increasing risk of chronic conditions over time would also be expected in the general population and thus it is important to compare these findings with a control group wherever possible to quantify the level of excess risk. Amongst the condition categories assessed, survivors were at particular risk of chronic health conditions due to cardiac[86,88,89], respiratory[88,89], endocrine[86,88,89], and neurologic causes[88,89].

2.1.2.3.1. Cardiac Conditions

Survivors of childhood cancer are at an increased risk of coronary artery disease, cardiomyopathy/congestive heart failure, pericardial disease, arrhythmias and valvular abnormalities when compared to a sibling control group[86,91,92]. Adverse effects of radiation and chemotherapy on cardiac function have been widely documented[10,12]. Radiation to the chest, mantle, or spine is associated with valvular dysfunction, pericarditis, and coronary artery disease[93–95]. Survivors of Hodgkin lymphoma treated with mediastinal radiation have the highest reported risk of radiation-associated cardiovascular disease and cardiac death among childhood cancer survivors[96,97]. Similarly, anthracycline chemotherapy has been associated with dose-dependent cardiotoxicity resulting in cardiomyopathy/heart failure[98] and arrhythmias[99]. In a study by Steinherz and colleagues, 11% of survivors had congestive heart failure following anthracycline doses of less than 400 mg/m^2 [100]; this percentage increased to 100% among individuals treated with anthracyclines at doses of more than 800 mg/m^2 [100]. Furthermore, in a Dutch study of approximately 600 survivors, the risk of anthracycline-

induced heart failure was found to increase over time, ultimately reaching approximately 5% at 15 years after treatment[101], which corresponds with two other previous reports[102,103]. These findings are similar to an American study which reported a cumulative incidence of 4% at 30 years after diagnosis[92]. Notably, in both the Dutch and America studies, the cumulative incidence did not plateau, but rather appeared to accelerate with age[92,101]. Although adverse cardiac health conditions have been documented up to 30 years after diagnosis, little is known about the risk in the longer term as survivors reach the decades of life when the risk of cardiac disease begins its inexorable increase in the general population. Cardiac health conditions remain one of the leading causes of morbidity and mortality in childhood cancer survivors and thus it is important to continue to monitor survivors and use the evidence to update clinical follow-up guidelines in order to determine the best strategies for early detection or prevention of such diseases.

2.1.2.3.2. Respiratory Conditions

The lung is sensitive to both radiation and chemotherapy[104]. Early treatment-induced lung disease (occurring two to six months after exposure) among childhood cancer survivors has been characterized as an acute phase of radiation pneumonitis and/or chemotherapy-induced interstitial lung injury, whilst the late effects of treatment generally present as pulmonary fibrosis[10,12,42,105]. Exposure to chest irradiation[42,106,107], bleomycin[42,105], mitromycin-C[105], nitrosoureas[42,105], busulfan[42,105], and cyclophosphamide[42,105,108] have been previously linked to pulmonary toxicity. In a large American study assessing respiratory complications after childhood cancer, survivors reported an increased risk of lung fibrosis, emphysema, pneumonia, chronic cough, bronchitis, and several other respiratory conditions compared to a sibling cohort[42]. Chest irradiation was found to be significantly associated with ten of the

fifteen respiratory conditions under investigation in the study, although nitrosoureas, bleomycin, busulfin, and cyclophosphamide were each associated with at least one condition[42]. As time since diagnosis increased, the incidence of respiratory complications also continued to increase[90], with survivors exposed to chest irradiation and respiratory toxic chemotherapy being the greatest at risk, followed by survivors exposed to chest irradiation only[42]. When assessed by diagnostic group, impaired respiratory function due to antineoplastic treatment has been previously reported in survivors of childhood leukemia[109–111], rhabdomyosarcoma[112], Wilms[106,107], CNS tumors[113], and Hodgkin lymphoma[114–116]. Although research has assessed respiratory complications up to 25 years past diagnosis, further research is needed on later adverse respiratory outcomes, especially as it is known that chemotherapy and radiation exposure can cause complications many years after treatment[42].

2.1.2.3.3. Endocrine Conditions

Among the spectrum of chronic health complications due to cancer treatment, endocrine abnormalities are the most common, inflicting a negative impact on quality-of-life, sexual function, growth, and body image[12]. In particular, neuroendocrine abnormalities may arise from damage to the hypothalamic-pituitary axis, which is vulnerable to certain tumors, radiation, chemotherapy, and surgical trauma[10]. Hypothalamic-pituitary axis injury has been widely studied, with increased risks of growth hormone deficiency[117–123], hypothyroidism[124,125], hyperthyroidism[124], gonadal dysfunction[118,125–131], and other endocrine disorder being reported widely among survivors of childhood cancer. In two studies from the United States and Australia, the proportion diagnosed with an endocrine (including reproductive) disorder was 62%[89,132]. When only severe, life-threatening, or disabling endocrine events were assessed, a Dutch study of over 1,300 childhood cancer survivors

reported a prevalence of 9% and 5% for fertility and endocrine disorders, respectively[88]. This high prevalence of dysfunction equated to approximately a five-fold increased risk of a severe, life-threatening, or disabling endocrine chronic condition when compared to a sibling cohort[90]. Survivors treated with radiotherapy to the head and neck reported an eight-fold increased risk of endocrine chronic conditions compared to those not exposed to radiotherapy[133]. An increased risk of endocrine chronic conditions was also observed for individuals treated with total body irradiation and radioactive iodine[133]. Similarly, when survivors exposed to alkylating agents and/or radiation to the hypothalamic-pituitary axis, thyroid, or reproductive organs were assessed in more detail, 61%, 14%, 66%, and 12% of survivors had disorders affecting the hypothalamic-pituitary axis, thyroid, male gonadal function, and female gonadal function, respectively[89]. Survivors of CNS tumors have been found previously to most likely to experience endocrinopathies[37,118,133], with 43% reporting one or more endocrine chronic conditions[37];individuals previously diagnosed with leukemia and Hodgkin lymphoma have also been reported to have increased risks of endocrine conditions, though[125]. Due to the fact that endocrine late effects are common, generally treatment-related, and progress to other chronic conditions, it is essential to further evaluate these outcomes to reduce the risk of morbidity and premature mortality whilst also improving quality-of-life[134].

2.1.2.3.4. Neurologic Conditions

Neurologic conditions, such as seizures, motor dysfunction/hemiparesis, and sensory loss, accounted for approximately 19% of all adverse chronic conditions observed in a study from the Netherlands[133]; 8% of the severe, life-threatening, and disabling chronic conditions observed were due to neurologic causes[133]. Similarly, when only severe, life-threatening,

disabling, or fatal neurologic events were assessed, an American study found that survivors of childhood cancer were approximately 4-times more at risk than the sibling comparison cohort[90]; the increased risk was highest among survivors aged 5-19 years (HR:10.6; 95%CI:5.8-19.3), when compared to the sibling cohort, although survivors aged 20-34 years and 35 or more years still had a statically significant increased risk of approximately two-fold[90]. Radiotherapy was associated with a more than two-fold increase in risk of neurologic chronic conditions[133], and survivors of CNS tumors[135–138] and acute lymphoblastic leukemia[139–144] were at increased risks of dysfunction due to therapy-related damage. Whist other nervous system abnormalities, such as neurocognitive and neuropsychologic outcomes, have been well documented in childhood cancer survivors[145], data is limited on neurologic complications. Neurologic morbidity continues to increase across the lifespan and thus there is a need for longitudinal, risk-based follow-up[90]. Furthermore, due to the strong treatment-dependent nature of neurologic chronic conditions, additional research may yield important findings on how morbidity may change with newer surgical, radiotherapy, and chemotherapy approaches.

2.1.2.4. Hospitalizations/Healthcare Usage

With such a high prevalence of chronic health conditions, increased hospitalizations or healthcare usage among childhood cancer survivors would also be expected. In a study of British childhood cancer survivors, the risk of non-hospital-based contact with a doctor was found to be only slightly increased among survivors compared to the general population sample[146]. However, in the same cohort, the risk was substantially higher among survivors compared to the general population sample for hospital outpatient, hospital day-patient, and inpatient care[146]. Results were similar in two Canadian studies that measured the prevalence

of contact with a general practitioner during the past year and hospitalizations[147,148]. A Scottish study that measured the risk of admission to acute hospitals also reported an increased risk, particularly among survivors of hepatic tumors, CNS tumors, leukemia, and neuroblastoma[149]. These findings are generally consistent with a different report which found that survivors of bone sarcoma and CNS tumors had the highest excess risks for outpatient and inpatient care, whilst survivors of Hodgkin lymphoma, neuroblastoma, and Wilms had the highest excess risk for being hospitalized as a day patient[146]. As the largest study to assess hospitalizations or healthcare usage in childhood cancer survivors was still limited in numbers of survivors in their 50s or 60s[146], it is important to continue to monitor the use of health care services as this population continues to age and experience more morbidities.

2.1.2.5. Health Related Quality-of-Life

Health related quality-of-life among childhood cancer survivors is affected by physical and psychological late effects associated with the original tumor and its treatment, as well as by the practical implications of the late effects. For example, the childhood cancer experience may lead to cognitive and psychological impairments, both of which may impact quality-of-life and impede post-treatment adjustment[60]. In a report of American childhood cancer survivors, approximately 11% reported fair or poor health, but 44% had an impairment in at least one of the health domains assessed[60]. When these individuals were compared to a sibling cohort and general population norms, survivors were found to report poorer physical and social health-related quality-of-life[59]. Mental health quality-of-life, however, has been reported to be similar if not better than expected from the general population[59,150]. Survivors of CNS tumors[59,60,62,150], lymphoma[59,60,151], bone sarcoma[59,60,150], and soft tissue sarcomas[59,60] have been reported to have the poorest health related quality-of-life. Other risk factors for

poor health related quality-of-life include being female[59,60,152–155], older in age[59,153], having a low educational attainment[59,60,153], and cranial irradiation or surgery[60,154,155]. Due to the fact that childhood cancer survivors report deficits in health related quality-of-life, it is crucial to continue to monitor health status among this at risk population in order to facilitate recovery and optimize well-being throughout the lifespan.

2.1.2.6. Psychosocial Outcomes & Behaviors

Aspects of diagnosis, treatment, and recovery of childhood cancer may disrupt social developmental, emotional well-being, and academic progress – all of which may have further adverse psychosocial effects throughout the life course[55,105,156]. Although most childhood cancer diagnoses report relatively similar psychosocial outcomes as those observed in the general population or sibling comparison groups[10], the majority of survivors remain challenged in areas that relate to social adaptation due to the fact that the diagnostic groups reporting excess risks (e.g. CNS and leukemia) account for a large proportion of childhood cancer survivors[52,68,157]. Thus, it is crucial to understand the long-term psychosocial impacts of diagnosis and treatment in order to develop targeted interventions to prevent or improve adverse psychosocial outcomes and behaviors, particularly those relating to educational attainment, employment, marriage, smoking status, and alcohol habits.

2.1.2.6.1. Educational Attainment

Educational attainment is a key element in determining an individual's development and progression through life[52]. Varying degrees of deficits have been reported among childhood cancer survivors in relation to educational attainment and diminished cognitive functioning. A study of British childhood cancer survivors found that survivors have lower educational

attainment than the general population[52]; however, upon further investigation, these deficits were confined to survivors of CNS tumors and leukemia[52]. Similar results were found in an American cohort[51]. Poor educational outcomes were also previously reported to be associated with earlier age at treatment[158–162], female gender[158,160,163–165], and cranial irradiation[158,159,161,165–168]. These findings illustrate the increased academic risk that childhood cancer survivors face and thus the need for interventions to improve educational outcomes[169].

2.1.2.6.2. Employment

After completing primary, secondary, or higher education, an important measure of normal development is employment[55,170]. Childhood cancer may impact employment status as survivors are at an increased risk of chronic diseases, mental and physical limitations, recurrences, and SPNs; these adverse health outcomes may influence the likelihood of an individual being able to work as it is known that, even in the general population, individuals with health limitations or disabilities are more likely to be unemployed[171]. When the likelihood of unemployment was assessed in a meta-analysis, the results showed that adult survivors of childhood cancer were twice as likely to be unemployed compared to controls[170]. Similarly, Pang et al. found that approximately 6% of American survivors had never been employed whilst only 1% was expected[172]. Risk factors for unemployment included a young age at diagnosis, cranial irradiation, female gender, and not finishing secondary schooling[172,173]. Survivors of CNS tumors were also reported to have the highest risk of unemployment at approximately five-fold that expected[170]. Given the excess risk in unemployment, clinical and supportive services are needed in order to better manage recovery and accommodate disabilities[170]. Furthermore, as the employment needs of survivors may

change over time, it is also important that future research also assesses specific employability and health reasons that are associated with obtaining and maintaining employment[173].

2.1.2.6.3. Marital Status

The majority of young adults in today's society aspire to marry[174]. Thus, marriage represents a social life-event that can be used to measure the adaptation of survivors to life beyond cancer[55]. Marital rates have been found to be lower in survivors of childhood cancer than expected in control populations[56,157,175–177]. Individuals exposed to radiotherapy[68,175] and males[50,157,175,177] appear less likely to marry than individuals not exposed to radiotherapy and females. Age at diagnosis[157,175], educational attainment[50,175], and income[175] have also been associated with likelihood of marriage. Furthermore, in reports from Great Britain and the United States, survivors of CNS tumors were found to be least likely to marry[68,175,178–180]. As childhood cancer survivors may face challenges in regards to relationships, it is important that regular follow-up also addresses the psychosocial needs of each survivor and that these factors are monitored throughout the life course. Nonetheless, it is reassuring that studies assessing divorce have found that survivors are generally comparable with the general population[175,180–183], although some reports have found an increased risk among specific diagnostic subgroups[176,180,182].

2.1.2.6.4. Smoking Status

As smoking is a major risk factor for a range of medical conditions, it is important that smoking is discouraged among childhood cancer survivors as they are already at an increased risk of adverse health outcomes due to their previous cancer and its treatment. In a study from Great Britain, approximately one-fifth of survivors reported being current smokers and

30% had smoked regularly at some point in their lives[70]. The smoking prevalence was similar in a study from the United States. When compared to the general population or healthy control subjects, a wide range of studies reported that survivors of childhood cancer were substantially less likely to smoke[73,184–190]. Although these findings are reassuring, studies have found that those who do smoke are less likely to quit when compared to siblings or other control subjects[184,186,187]. Thus, it is important that strategies are developed and integrated into long-term follow-up programs in order to prevent the initiation of smoking among childhood cancer.

2.1.2.6.5. Alcohol Habits

Studies assessing alcohol use in childhood cancer survivors have reported that these individuals are similar or less likely to be a current drinker when compared to the general population or sibling cohort[69,72,190–192]. Survivors were also less likely to consume excessive or risky amounts of alcohol compared to controls[69,72,185,190]. Although generally survivors appear to be living healthier lives compared to the general population in relation to alcohol use, survivors who have similar heavy drinking habits as the general population may have an even higher risk of a variety of late effects as alcohol could increase already heightened risks of SPNs and chronic conditions[6925,85,193,194]. For example, studies from the United States and Great Britain found that survivors of Hodgkin lymphoma, Wilms, and bone sarcoma reported similar adverse drinking behaviors as the comparative populations; these diagnostic groups are already at an increased risk of adverse outcomes due to their likely exposure to abdominal/chest irradiation and/or anthracycline drugs and thus excessive alcohol use may make these risks even higher[69,71]. Based on these findings, survivors should be advised on the health risks associated with alcohol consumption. It is particularly important that survivors

are aware of these risks at a young age as early alcohol consumption has been associated with heavier drinking later in life[72].

2.2. Teenage and Young Adult Cancer

2.2.1. Incidence and Survival

The age range for teenage and young adult cancer is defined in various ways across the world. At a national level, the United Kingdom describes teenage and young adult cancers as a cancer being diagnosed between the ages of 15 to 24 years[195]. Approximately 2,200 individuals are diagnosed each year with a teenage or young adult cancer in the United Kingdom, accounting for less than 1% of cancers at all ages[195]. The spectrum of diagnostic types of cancer affecting teenage and young adults differ from those in childhood and older populations[196] and thus are classified differently. Teenage and young adult cancers are generally classified according to the scheme proposed by Birch et al., which utilizes the following ten groups[197]: leukemias, lymphomas, CNS and other intracranial and intrapsinal neoplasms (CNS tumors), osseous and chrondromatous neoplasms, Ewing sarcoma and other neoplasms of bone (bone tumors), soft tissue sarcomas, germ cell and trophoblastic neoplasms (germ cell tumors), melanoma and skin carcinoma, carcinomas excluding skin, miscellaneous neoplasms, and unspecified malignant neoplasms (Figure 2.3). Leukemias, lymphomas, CNS tumors, bone and soft tissue sarcomas, testicular cancer, breast cancer, non-gonadal germ cell tumors, and melanoma account for approximately 95% of the cancers in this age group[196,198,199].

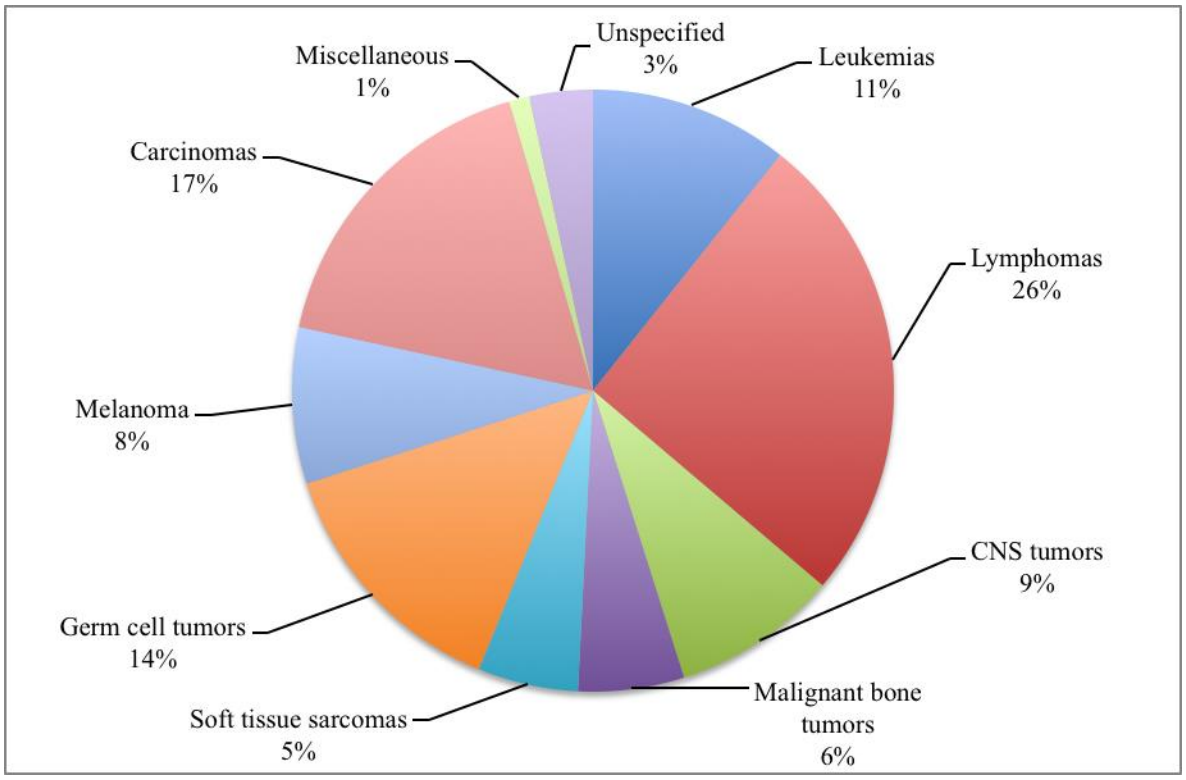

Figure 2.3: Main types of teenage and young adult cancer for individuals diagnosed with cancer between the ages of 15-24 years in England (1979-1997)[197]

Survival from cancer in teenagers and young adults has improved over time and is currently approximately 82%[200]. In the United Kingdom, five-year survival increased significantly from 75.7% to 82.2% among 15-24 year olds diagnosed with cancer in 1992-1996 and 2002-2006, respectively. When assessed further by diagnostic group, five-year survival was observed to increase for leukemias, lymphomas, germ cell tumors, and melanoma; five-year survival rates remained similar for CNS tumors, bone tumors, soft tissue sarcoma, and carcinomas (Figure 2.4)[195].

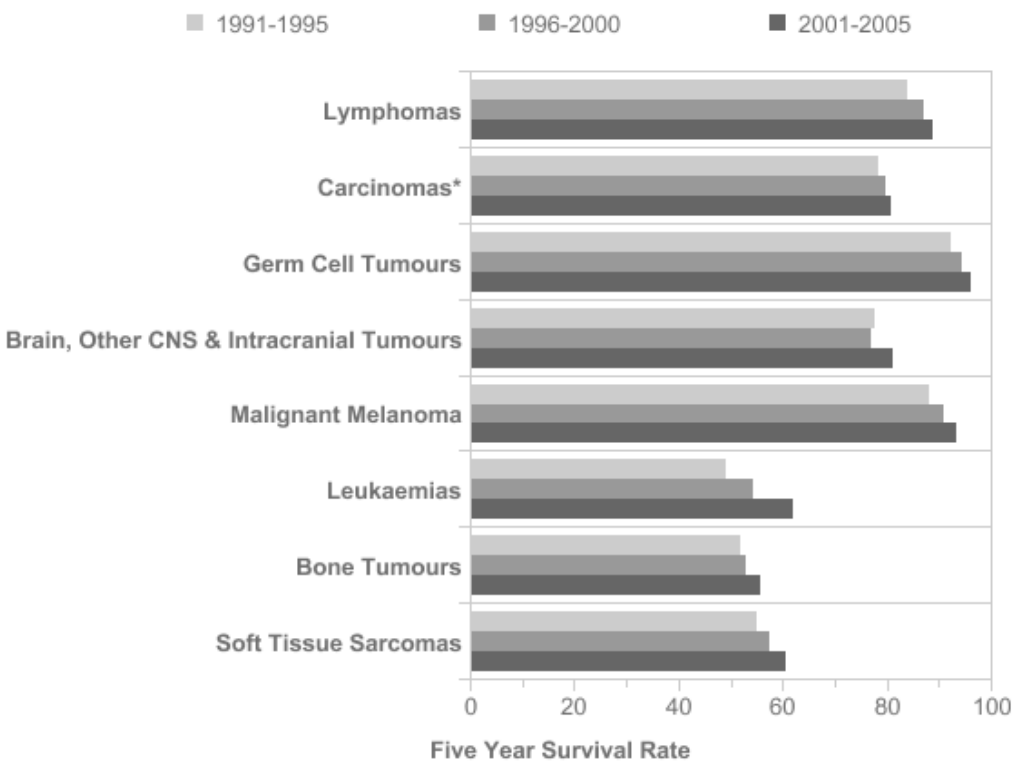

Figure 2.4: Five-year relative survival rates by diagnostic group for individuals diagnosed with cancer between the ages of 15-24 years (1991-2005)[195]

2.2.2. Long-term Follow-Up Guidelines

In contrast to childhood cancer, no standardized clinical guidelines for long-term follow-up exist for individuals diagnosed with a teenage or young adult cancer[201]. The most likely explanation for this absence of standardized clinical follow-up guidelines relates to the lack of evidence of risks of adverse health outcomes. Due to the paucity of published literature on teenage and young adult cancer, survivors instead receive care determined primarily by the opinion of their treating oncologists[201]. Due to the variability in opinions of oncologists, some survivors receive extended follow-up whilst others receive care through their oncologist for one to two years at which point they are then discharged to their general practitioner[201]. Follow-Up may be further disrupted due to other factors, such as insurance, employment

issues, geographical location, and lower levels of concern for future treatment-related morbidities[201]. As a result of the lack of standardized follow-up, most survivors are unaware of their risks of adverse health outcomes and some are not receiving adequate care. Thus, it is crucial to expand the literature on teenage and young adult cancers in order to develop the vital evidence needed to deliver risk-based health monitoring, psychosocial support, and interventions for current and future survivors of teenage and young adult cancer[201].

2.2.3. Adverse Late Effects

Among the limited current studies age definitions for teenage and young adult cancer vary, and thus for the purpose of this thesis teenage and young adult cancer will be defined as an individual diagnosed with cancer between the ages of 15 to 39 years. The lower age limit was determined by the definition for childhood cancer, which was described previously to include individuals diagnosed with cancer before the age of 15. The upper age limit was decided based upon biological and physiological maturity, which occurs around puberty, and achievement of final height, which remains fairly stable during an adult's 20s and 30s. Thus, the effects of hormonal decline, diminishing immunity, and increasing development of chronic diseases of adulthood should be largely insignificant among those aged less than 40 years. Individuals under the age of 40 years are also more likely to identify psychologically with younger patients than more mature patients. Furthermore, previous literature has suggested that the late effects of cancers diagnosed before age 40 years may substantially differ from older populations, and thus it is important to analyze this group separately as radiotherapy, chemotherapy, and surgery may have different effects among those diagnosed at an older age[202,203]. By including all cancers between the ages of 15 to 39 years, our findings will provide comprehensive evidence for improving outcomes for teenage and young adult

cancer survivors because we partially or entirely encompass the more limited age ranges used in previous studies of survivors of teenage and young adult cancer.

Limited studies so far suggest that teenage and young adult cancer survivors are at an increased risk for late effects due to their cancer and treatment received, with approximately two-thirds of survivors experiencing at least one late effect that is severe or life-threatening[201,204–206]; however, the degree of risk depends on the type of cancer, treatment received, and age at diagnosis. Risks may be further influenced by factors such as lifestyle behaviors, family history, and health comorbidities[196]. Studies have previously shown in sub-populations of teenage and young adult cancers that these individuals are at an increased risk of premature mortality, SPNs, chronic health conditions, and adverse psychosocial outcomes[201]. However, to date, research assessing adverse late effects for the entire age range of teenage and young adult cancers is limited, with the majority of studies assessing patients diagnosed up to the ages of 21 or 24 years[196]. As a large proportion of teenage and young adult survivors are now surviving at least five years, it is crucial to monitor the long-term outcomes that may be affected by cancer and its treatment in order to improve outcomes in these individuals through appropriate guidelines and clinical interventions.

2.2.3.1. Premature Mortality

Few studies have investigated premature mortality in teenage and young adult cancer survivor populations[207–210]. In a study assessing premature mortality among five-year survivors of teenage and young adult cancers in Finland, survivors of cancers diagnosed when aged 15 to 19 years were 6-times more likely to die than expected, whilst those aged 20 to 34 years at diagnosis were 5-times more at risk than expected[209]. These findings were similar to a study

conducted in Canada, which reported a six-fold increased risk of death among survivors of cancer diagnosed between the ages of 20 to 24 years[208]. In absolute terms, the most frequent cause-of-death among teenage and young adult cancer survivors was neoplastic causes followed by cardiovascular complications[207,211]. Similarly, when the excess risk was assessed, the risk of death was highest for neoplastic causes, infectious causes, cardiovascular diseases, and respiratory diseases[207]. Risk of death was observed to decrease with age at diagnosis; survivors diagnosed between the ages of 15 to 19 years experienced 25-fold and three-fold the number of deaths from neoplastic and non-neoplastic causes, respectively, whilst the corresponding risk for those aged 20 to 34 at diagnosis was 14-fold and two-fold[209]. These findings clearly confirm an already increased risk and need for monitoring of late effects among teenage and young adult cancer survivors; they also illustrate the need for teenage and young adult focused studies, as assessment of premature mortality and generalizability of results are still limited.

2.2.3.2. Subsequent Primary Neoplasms

Compared to the general population, survivors of teenage and young adult cancers are at a significantly higher risk of developing a SPN[201,212]; however, the majority of these studies were restricted by the age range or diagnostic group assessed. In individuals aged 15 to 21 years at diagnosis, the risk of SPNs was greatest for breast cancer, non-melanoma skin cancers, and other solid organ cancers[213,214]. Among individuals treated for Hodgkin lymphoma between the ages of 21 to 39 years, the most frequently observed SPNs were breast, thyroid, lung, and gastrointestinal cancers[215]; female survivors of Hodgkin lymphoma who were treated with chest irradiation have been shown to have a substantially increased risk of breast SPNs, and there is a strong interaction between chest irradiation and age at

diagnosis[202,203,216,217]. Alkylating chemotherapeutic agents have also been associated with a moderately increased risk for lung SPNs in Hodgkin lymphoma survivors originally diagnosed before the age of 40 years[218]. Teenage and young adult survivors of testicular cancer have also been found to be at an increased risk for SPNs, particularly leukemia, contralateral testicular cancer, malignant mesothelioma, and cancers of the esophagus, lung, stomach, colon, and pancreas[219,220]. Studies assessing SPN risk in teenage and young adult survivors of breast, cervical, NHL, melanoma, leukemia, CNS tumors, bone sarcoma, and soft tissue sarcoma have been limited, with only a few cohorts assessing these risks[212,221–225]; nonetheless excess risks were observed compared to that expected for all diagnostic groups[201]. As risks of SPNs among teenage and young adult survivors remain understudied, it is essential that further investigations are undertaken in order for clinicians to provide appropriate evidence-based care.

2.2.3.3. Chronic Health Conditions

Investigations assessing chronic health conditions among teenage and young adult cancer survivors are few. As it is known that childhood cancer survivors are at an increased risk of chronic health conditions due to their cancer and its treatment, one can hypothesize that these risks likely exist among teenage and young adult cancer survivors as well. However, the majority of studies investigating chronic health conditions assess only one diagnostic group or use a very restricted age at diagnosis range. A study in Scotland found that individuals diagnosed with cancer from 15 to 19 and 20 to 24 year were 3.5- and 2.4-times more likely than expected to be hospitalized, respectively, suggesting an increased risk of chronic health conditions[149]. Other studies have also reported increased risks of cardiovascular[92,226–233],

respiratory[234], endocrine[194,234–237], and neurologic[136,194,238,239] conditions, which will now be explored further.

2.2.3.3.1. Cardiac Outcomes

Significant increases in cardiovascular morbidity have been reported in survivors of teenage and young adult cancers[92,201,226–230]. In a study assessing cardiovascular disease in over 40,000 survivors of cancer diagnosed between the ages of 15 to 39 years in Denmark, approximately 25% of survivors had been admitted to the hospital for a cardiovascular cause, which equated to a 30% increased risk of cardiac hospitalization compared to the general population[227]. A study from Finland also reported significantly increased risks of cardiovascular morbidity in teenage and young adult survivors (aged 20 to 34 years) compared to siblings, where risks of cardiomyopathy/cardiac insufficiency, myocardial infarction/cardiac ischemia, atherosclerosis/brain vascular thrombosis, and cardiac arrhythmia were 3.6-, 1.8-, 1.7-, and 1.4-times higher than that expected, respectively[210]. Chest irradiation and anthracycline chemotherapy are the strongest risk factors for adverse cardiac outcomes among survivors[92,228–230]. Survivors of Hodgkin lymphoma[210,228–230] and testicular cancer[231–233] have also been reported to have increased risks of adverse cardiac outcomes likely due to effects of radiotherapy and chemotherapy treatment. As cardiovascular disease is the leading cause of non-neoplastic morbidity and mortality in teenage and young adult cancers, further investigation is necessary in different study populations in order to provide more complete evidence on which to base clinical recommendations.

2.2.3.3.2. Respiratory Outcomes

Recurrent pneumonia, chronic cough, supplemental oxygen use, and shortness of breath are all adverse respiratory outcomes that teenage and young adult cancer survivors face[196]. In a study of cancer survivors diagnosed between the ages of 20 to 24 in Canada, survivors were 70% more likely to be hospitalized for a respiratory-related cause compared to the control population[234]. Chest irradiation and chemotherapy drugs, such as bleomycin, busulfan, BCNU, and CCNU, have been linked to pulmonary toxicity when used together or individually[42,201,232,240–242]. Research into respiratory outcomes remains understudied in teenage and young adult cancer survivors; as childhood cancer survivors are at a known increased risk of adverse respiratory conditions, investigations into this matter for survivors of cancer diagnosed when older is necessary in order to identify at risk populations and make appropriate evidence-based recommendations for follow-up.

2.2.3.3.3. Endocrine Outcomes

Hypopituitarism, or being deficient of one or more anterior pituitary hormones (growth hormone, follicle-stimulating hormone, luteinizing hormone, adrenocorticotrophic hormone, or thyroid-stimulating hormone), can occur as a result of the cancer directly or the treatment used[201]. Survivors of teenage and young adult cancer in Canada were approximately 60% more likely to be hospitalized for an endocrine condition than controls[234]. The most common chronic endocrine conditions in survivors of teenage and young adult cancers were growth hormone deficiency, gonadal dysfunction, decreased fertility, and thyroid gland abnormalities[236,237]. Total body irradiation, cranial or spinal irradiation, and irradiation to the neck, abdomen, pelvis, and testes were associated with chronic endocrine conditions in teenage and young adult cancer survivors[243]. Hypothyroidism and hyperthyroidism, however,

were also common among teenage and young adult survivors of CNS tumors, acute lymphoblastic leukemia, and Hodgkin lymphoma[194,235]. Currently, chronic endocrine conditions among teenage and young adult cancer survivors are an understudied topic and further investigation is necessary.

2.2.3.3.4. Neurologic Outcomes

Neurologic complications among teenage and young adult survivors have not been investigated widely, but the limited literature published has identified specific groups to be at an increased risk of neurologic sequelae[196]. For example, in a study assessing American teenage and young adult survivors aged 15 to 21 years, individuals treated with cranial radiotherapy were found to be at an increased risk for neurologic complications, such as seizure disorders, coordination and motor control problems, hearing impairments, and cataracts[194,238]. Survivors of testicular cancer treated with cisplatin-based chemotherapy agents have also been shown to be at an increased risk of sensory neurologic complications, with 29% reporting paresthesia of the hands or feet, 22% reporting tinnitus, and 21% reporting hearing impairments[244]. Finally, increased risk of stroke has been associated with cranial irradiation in CNS tumor and leukemia survivors and mantle field irradiation in Hodgkin lymphoma survivors[136,239]. Further studies are needed to assess neurologic outcomes in teenage and young adult populations in order to make more suitable evidence-based recommendations for survivors.

2.2.3.4. Psychosocial Outcomes & Behaviors

Individuals treated for a cancer as a teenager or young adult face different psychosocial outcomes than survivors of cancer diagnosed in childhood or mature adulthood[245,246]. In

particular, survivors treated in teenage and young adulthood need to cope with having cancer and its treatment whilst developing their personal and sexual identity, maintaining their peer involvement, and establishing their autonomy[161,247]. Due to the fact that cancer is associated with lengthy treatments, cancer can often disrupt these developmental milestones, which in return may impact school, work, and relationships, and ultimately cause negative consequences for long-term financial status and career opportunities[196,248]. Cancer-related issues, such as loss of fertility or confrontation with potential mortality, may also lead to emotional distress and psychiatric symptoms[196]. Recent studies assessing emotional issues found that psychological distress was significantly higher among teenage and young adult cancer survivors compared with survivors of cancer diagnosed in older adulthood[249–251] or age-matched peers[252]. Psychological problems were also associated with an increased risk for obesity and other poor health-related behaviors, such as tobacco, alcohol, or substance use[196]. Thus, psychosocial counseling and support is necessary across the life course in order to assist teenage and young adult survivors of cancer with accepting cancer, maintaining an active and independent life, coping with treatment-side effects and stress, and maintaining a positive attitude[196,248].

2.3. Study Populations

2.3.1. British Childhood Cancer Survivor Study

The British Childhood Cancer Survivor Study (BCCSS) is a large, population-based study of childhood cancer survivors who survived at least five years. The cohort was ascertained by using the population-based National Registry of Childhood Tumours (NRCT), which has approximately a 99% ascertainment rate[253]. Demographic, cancer, and treatment-related factors were provided for all survivors by NRCT. The BCCSS was established as a

consequence of the improvements in childhood cancer survival rates across recent decades, which has led to a growing population of living childhood cancer survivors. As it is internationally recognized that survivors of childhood cancer are a high-risk population with specific health care needs[254], it was imperative that these individuals be monitored for long-term outcomes, especially as these survivors have many decades of life remaining due to their young age at diagnosis. Thus, the main objective of the BCCSS is to assess adverse health and social outcomes following childhood cancers[255]. Ethical and legal approval for the BCCSS was given by a Multi-Centre Research Ethics Committee and every Local Research Ethics Committee in Britain.

Originally, to be eligible for inclusion, survivors had to be diagnosed with cancer in Britain before the age of 15 years, between January 1, 1940 and December 31, 1991, and to have survived at least five years from their original cancer diagnosis. The overall eligible population-based cohort comprised 17,980 survivors. These individuals were then linked to the Health and Social Care Information Centre, which are maintained at Southport (England and Wales) and Edinburgh (Scotland)[255]. Through this linkage, three critically important types of information were obtained for all individuals in the BCCSS cohort. Firstly, the vital status of each survivor was obtained by linking with the national death registration system. Secondly, all SPNs were identified by linking with the national cancer registration system. And, finally, the current general practitioner practice was identified for all survivors who were alive.

By ascertaining each survivor's National Health Service status, the Study Coordinating Center was then able to identify the survivor's current primary care physician. Using the primary

care physician's details, a study package was then sent to all survivors who were alive, a British resident, and aged at least 16 years at time of questionnaire send out (median year 2002). The study package to the primary care physician contained the following items: (1) a covering letter indicating the need for the study and seeking their cooperation, (2) a consent form for the primary care physician to give their permission for their patient, the survivor, to be included in the study together with a reply paid enveloped addressed to the Study Coordinating Center, (3) a suggested draft letter for the primary care physician to send to the survivor with the study questionnaire inviting participating, and (4) a postage-paid package to be mailed to the survivor by the primary care physician after the inclusion of the suggested draft letter[255]. The package of documents sent to the survivors contained the following items: (1) the suggested covering letter from the primary care physician inviting participation, (2) a covering letter from the Study Coordinating Center, (3) a short explanatory leaflet for the survivor, (4) a personalized copy of the study questionnaire in either the male or female version depending on the sex of the survivor, and (5) a reply paid envelope for the survivor to return the completed questionnaire to the Study Coordinating Center[255]. Ethical approval for the questionnaire send-out was obtained from a Multi-Centre Research Ethics Committee and every Local Research Ethics Committee in England, Wales, and Scotland.

Of the 17,980 total survivors in the BCCSS cohort, 14,880 (82.8%) were alive, a British resident, and aged at least 16 years at questionnaire send out. Of those who were ineligible for a questionnaire, 2,780 (15.5%) had died subsequent to surviving at least five years, 245 (1.4%) had emigrated, and 75 (0.4%) were alive, a British resident and under 16 years age[255]. An additional 45 survivors were excluded from receiving a questionnaire because they were not traced with the Health and Social Care Information Centre (n=24), adopted subsequent to

diagnosis of childhood cancer (n=16), or had indicated as part of a pilot study that they did not want to be contacted again (n=5)[255]. Thus, ultimately, 14,835 survivors were available to receive a postal questionnaire survey[255].

In total, 10,488 completed questionnaires were returned to the Study Coordinating Center, which equated to a response rate of 70.7%. Each questionnaire contained a range of questions relating to the survivor's life, including topics such as health status, marriage, pregnancies and children, family history, smoking and alcohol use, educational attainment, employment, life and medical insurance, and personal concerns. The full male and female questionnaires can be found in Appendix 1 and Appendix 2, respectively.

In 2014 the BCCSS was subsequently extended to include individuals diagnosed with childhood cancer from January 1, 1992 to December 31, 2006 in Britain and who had survived at least five years from their childhood cancer. Ethical and legal approval was given by the National Research Ethics Service (NRES) and national Confidentiality Advisory Group (CAG). With the extension, the BCCSS comprises 34,489 five-year survivors of childhood cancer. Information relating to vital status and SPNs is available for all survivors in the cohort. Information on social, economic, and health outcomes is available for only the survivors who completed the questionnaire survey (n=10,488). This thesis includes analyses on the BCCSS both before and after the extension; however, the study population under investigation will be described in the methods section of each of the subsequent chapters. Baseline characteristics of the original and extended cohorts can be found in Appendix 3.

2.3.2. Teenage and Young Adult Cancer Survivor Study

The Teenage and Young Adult Cancer Survivor Study (TYACSS) is a large, population based study of individuals diagnosed with cancers between the ages of 15 to 39 and who have survived at least five years[256]. The cohort was established in collaboration with the Office for National Statistics (ONS) and Welsh Cancer Registry due to the international acknowledgement of the need for survivorship and late effects studies relating to individuals diagnosed with cancer as teenagers and young adults[6,256–261]. As cancer incidence rates take up to five years after the end of a given calendar year to reach 100%[262], ascertainment for this cohort is expected to be essentially complete as the upper limit for diagnosis inclusion was 2006. Ethical and legal approval for the TYACSS was given by the National Research Ethics Committee and Confidentiality Advisory Group.

In order to be included in the TYACSS cohort, individuals had to be diagnosed with a teenage or young adult cancer from January 1, 1971 to December 31, 2006 in England or Wales and survive at least five years. The total eligible population-based cohort comprises 200,945 survivors. These individuals were then linked to the Health and Social Care Information Centre, which provided the vital status of each survivor, via the national death registration system, and all cancer registrations, via the national cancer registration system. Baseline characteristics of the TYACSS cohort can be found in Appendix 4.

2.4. Thesis Outline and Aims

This thesis aims to expand upon the current understanding of late adverse effects among five-year survivors of childhood, teenage, and young adult cancers through the investigation of five studies using the two cohorts described above. Such large population-based

investigations of risks of a wide spectrum of fatal and non-fatal adverse health outcomes provide the most reliable, unbiased, and comprehensive evidence base for (i) counseling, educating, and empowering survivors, (ii) providing educational material for healthcare professionals, (iii) constructing survivorship care plans, (iv) providing risk stratification evidence to inform decisions on amending (childhood cancer) and developing (teenage and young adult cancer) clinical follow-up guidelines, (v) advising the Department of Health in relation to groups at sufficiently elevated risk to consider recall for counseling, screening, or other interventions, (vi) identifying low risk groups for discharge from hospital follow-up, (vii) evaluating risks and benefits of proposals for future treatment protocols, and (viii) health economic evaluations.

The specific aims of this thesis are:

1. Study 1: To assess a wide range of adverse health (mortality, SPNs, hospitalizations/healthcare usage, quality-of-life) and social (educational attainment, marital status, alcohol and smoking habits) outcomes among five-year survivors of childhood bone sarcoma within the BCCSS cohort.
2. Study 2: To assess aspects of mental health dysfunction among five-year survivors of childhood cancer within the BCCSS cohort.
3. Study 3: To quantify the risk of late cause-specific mortality among five-year survivors of childhood cancer within the BCCSS extended cohort.
4. Study 4: To quantify the risk of cardiac mortality among five-year survivors of childhood cancer within the BCCSS extended cohort.

5. Study 5: To quantify the risk of respiratory mortality among five-year survivors of childhood, teenage, and young adult cancers within the BCCSS and TYACSS cohorts.

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CHAPTER 3

STUDY 1:

Long-term adverse outcomes in survivors of childhood bone sarcoma

Abstract

Purpose: With improved survival, more bone sarcoma survivors are approaching middle age making it crucial to investigate the late effects of their cancer and its treatment. We investigated the long-term risks of adverse outcomes among five-year bone sarcoma survivors within the British Childhood Cancer Survivor Study.

Material and Methods: Cause-specific mortality and risk of subsequent primary neoplasms (SPNs) were investigated for 664 bone sarcoma survivors. Use of health services, health and marital status, alcohol and smoking habits, and educational qualifications were investigated for survivors who completed a questionnaire.

Results: Survivors were seven-times more likely to experience all-cause mortality than expected, and there were substantial differences in risk depending on tumor type. Beyond 25 years follow-up the risk of dying from all-causes was comparable to the general population. This is in contrast to dying before 25 years where the risk was 13-fold that expected. Survivors were also four-times more likely to develop a SPN than expected, the excess restricted to 5-24 years post-diagnosis. Increased healthcare usage and poor health status were also found. Nonetheless, for some psychosocial outcomes survivors were better off than expected.

Conclusions: Up to 25 years after five-year survival, bone sarcoma survivors are at substantial risk of death and SPNs, but this is greatly reduced thereafter. As 95% of all excess deaths before 25 years follow-up were due to recurrences and SPNs, increased monitoring of survivors could prevent mortality. Furthermore, bone and breast SPNs should be a particular

concern. Since there are variations in the magnitude of excess risk depending on the specific adverse outcome under investigation and whether the survivors were initially diagnosed with osteosarcoma or Ewing sarcoma, risks need to be assessed in relation to these factors. These findings should provide useful evidence for risk stratification and updating clinical follow-up guidelines.

Introduction

Primary malignant bone sarcomas account for 4.8% of all childhood cancers in the UK[1]. Approximately 65 cases occur each year, of which the principal tumor types are osteosarcoma (53%) and Ewing sarcoma (39%)[1]. Although the incidence is low, survival after bone sarcoma has increased substantially. Since the 1970s five-year survival has risen from 23% to 64% mainly due to the introduction of modern chemotherapy[1]. Consequently, as the number of individuals treated for childhood bone sarcomas increases, it becomes ever more important to investigate the risk of the long-term effects of this childhood cancer and its treatment.

This study assessed adverse outcomes among bone sarcoma survivors diagnosed between the ages of 0-14 years within the British Childhood Cancer Survivor Study (BCCSS). Key advantages of the BCCSS compared to other studies are that it is a large, population-based cohort with 30.4% of individuals diagnosed with bone sarcoma surviving to age 45 years at least. Therefore, adverse health and social outcomes beyond 35 years post-diagnosis in these childhood cancer survivors can be examined much more satisfactorily than has been possible in previous smaller or non-population based studies with limited follow-up[2–6]. In this study, we investigated the long-term risk of premature mortality, developing a subsequent primary neoplasm, healthcare usage, health and marital status, alcohol and smoking habits, and educational attainment among five-year childhood bone sarcoma survivors.

Material and Methods

British Childhood Cancer Survivor Study

The BCCSS, which has been described previously in detail[7], is a population-based cohort comprised of 17,980 individuals; it includes 664 bone sarcoma survivors diagnosed with cancer before the age of 15, between 1940-1991 in Great Britain, and who have survived at least five years. The cohort was ascertained through the National Registry of Childhood Tumours, which has a high estimated level of completeness (~99%)[8]. Ethical approval for the study was obtained from a Multi-Centre Research Ethics Committee and every Local Research Ethics Committee in Britain.

When treatment exposures within this cohort were investigated across five-year calendar year bands, we found that prior to 1976, where our radiotherapy and chemotherapy treatment completeness was 98.4% and 88.4% respectively, the majority of bone sarcoma survivors received radiotherapy (76.3%), with only a small proportion receiving chemotherapy. A distinct change in treatment practice was then observed from 1976 onwards where broadly all survivors received chemotherapy and Ewing sarcoma survivors additionally received radiotherapy. Thus, in order to address the incompleteness of treatment information in more recent diagnosis years, which was due to decreasing availability of recorded radiotherapy and chemotherapy details at the National Registry of Childhood Tumours during this period, our analyses were undertaken for bone sarcoma survivors overall and separately for osteosarcoma and Ewing sarcoma, which serve as proxies for treatment exposures. Therefore, osteosarcoma survivors were likely to have received radiotherapy if diagnosed prior to 1976 and only chemotherapy if diagnosed from 1976 onwards, whereas all Ewing sarcoma survivors were likely to have received radiotherapy, with only those diagnosed after 1976 additionally

receiving chemotherapy. Consequently, those surviving beyond 25 years from five-year survival were likely to have only received radiotherapy, whilst those with less than 25 years follow-up were likely to have received only chemotherapy or chemotherapy and radiotherapy depending on tumor type.

Record Linkage Ascertained Outcomes

Deaths and subsequent primary neoplasms (SPNs) were ascertained for the entire BCCSS cohort through record linkage with the Health and Social Care Information Centre, which includes the population-based national death and cancer registries. This linkage ensures that the BCCSS is notified whenever a survivor has died or developed a SPN. To determine the expected number of deaths or incident cancers, person-years for each sex-specific, age-specific (five-year bands), and calendar year-specific (one-year bands) stratum were multiplied by the corresponding general population rates for specific cause(s)-of-death and incident cancers occurring throughout England and Wales.

Cause-specific Mortality

For our mortality analysis, the death certificate and underlying cause-of-death, as coded by the Office for National Statistics using the relevant *International Classification of Disease,* were obtained. The underlying cause-of-death was then confirmed by a clinician using available medical records; very little disagreement was observed and thus the underlying cause-of-death listed on the death certificate was utilized. Time at risk started at five-year survival and continued until individuals exited from risk at the first occurrence of emigration, death, or December 31, 2010, which was the date of the most recent vital status update on the entire cohort from the National Health Service Information Centre. The standardized

mortality ratio (SMR) was defined as the ratio of observed to expected number of deaths. The absolute excess risk (AER) was defined as the observed minus the expected number of deaths divided by person-years at risk multiplied by 10,000. Cumulative mortality for a specific cause-of-death was calculated by treating other causes-of-death as competing risks.

Subsequent Primary Neoplasms

Confirmation of all SPNs was undertaken by writing to the relevant clinician(s) to obtain diagnostic reports to confirm site, type, and date of diagnosis. Irrespective of further clinical input or information, the SPN site and type coded at cancer registration was used. Time at risk for a SPN began at five-year survival and individuals exited from risk at the first occurrence of an SPN, emigration, death, or December 31, 2006 which was the most recent date up to which all potential SPNs had been ascertained and validated. Standardized incidence ratios (SIRs) were calculated as the ratio of observed to expected number of neoplasms. AERs were calculated as described previously for the mortality analyses. Cumulative incidence for the first occurrence of a SPN was computed treating death as a competing risk.

Questionnaire Ascertained Outcomes

Healthcare usage, health and marital status, alcohol and smoking habits, and educational attainment were obtained via the BCCSS questionnaire. To be eligible to receive the BCCSS questionnaire survivors in the cohort had to be alive and aged at least 16 years at questionnaire send-out (median year 2002). Of the 664 bone sarcoma survivors, 506 survivors met this eligibility criteria and were contacted; amongst survivors who were ineligible, the majority had died prior to questionnaire send-out (n=106). Ultimately, 411

(81.2%) returned a completed questionnaire. All comparisons with the general population were adjusted for age and sex. Some outcomes were adjusted further – see tables for details.

Healthcare Usage

Four types of healthcare usage were assessed: talking to a doctor, attending the hospital outpatient department, being hospitalized as a day patient, and being hospitalized as an inpatient. In order to compare healthcare use with the general population, the 2002 General Household Survey (GHS) served as the general population sample[9]. Multivariable generalized estimating equation (GEE) logistic regression modeling was used to calculate odds ratios (OR) for healthcare usage among bone sarcoma survivors compared to that expected from the general population sample[10].

Psychosocial Outcomes

The survivors' education level, smoking history, and alcohol consumption were compared to the general population using the 2002 GHS[9] as the reference sample, whereas marital status was compared to the National Marriage Registry[11]. Multivariable GEE logistic regression was used to compare educational attainment, smoking status, and alcohol use between survivors and the general population sample[12–14]. ORs were calculated using pooled Mantel-Haenszel tests to compare marital status between survivors and the general population sample.

Health Status

Version one of the Short Form 36 (SF-36) Health Survey was used to measure self-reported health status by the following eight scales: physical function, role-physical, role-emotional, social functioning, mental health, vitality, pain, and general health perception. External

comparisons were conducted using the Oxford Healthy Life Survey (OHLS) as the general population sample. Multivariable linear regression and direct standardization were used to compare bone sarcoma survivors and the OHLS population.

All analyses were undertaken using Stata 12.1[15]. Statistical significance was defined as a two-sided *P*-value less than 0.05.

Results

Study Characteristics

Of the 664 bone sarcoma survivors, 309 (46.5%) were diagnosed with osteosarcoma, 260 (39.2%) were diagnosed with Ewing sarcoma, 26 (3.9%) were diagnosed with chondrosarcoma, 48 (7.2%) were diagnosed with other specified bone sarcomas (e.g. fibromatous neoplasms, giant cell tumors, chordomas, miscellaneous bone tumors), and 21 (3.2%) were diagnosed with an unspecified bone sarcoma. The mean age at diagnosis was 10.8 and the average attained age was 39.4 years (**Table 3.1**). Osteosarcoma survivors were older at diagnosis and had a higher attained age compared to Ewing sarcoma survivors. Excluding missing information, 60.2% and 60.0% of survivors received radiotherapy and chemotherapy, respectively. In general, characteristics of the 411 survivors who returned a questionnaire were similar both overall and by tumor type to the entire BCCSS bone sarcoma cohort, except that only 3.7% had died by December 31, 2010 subsequent to completing a questionnaire.

Record Linkage Ascertained Data

Cause-specific Mortality

Overall, bone sarcoma survivors experienced seven-times (SMR:7.0, 95%CI:5.9-8.3) the number of deaths expected from the general population with 72 (95%CI:57.2-85.8) excess deaths per 10,000 person-years (**Table 3.2**). The largest excess was for neoplastic-related causes in both relative and absolute terms; recurrences and SPNs accounted for 71.2% and 22.6% of all excess deaths, respectively. When the SMR was assessed by follow-up, a striking difference was observed; the overall SMR was 12.7-times (95%CI:10.5-15.2) that expected during 0-24 years follow-up and only 1.7-times (95%CI:1.0-2.7) that expected

beyond 25 years. Notably, there was an eight-fold decrease in SMRs from 0-24 years to beyond 25 years follow-up for SPN-related deaths. Compared to the general population, the SMR for all-causes was significantly higher (P<0.001) for Ewing sarcoma survivors, who had approximately double the SMR and AER of osteosarcoma survivors. Although recurrence and SPN related deaths accounted for approximately 93% of all excess deaths in both tumor types, there was heterogeneity in the proportion of recurrence and SPN excess deaths; recurrences accounted for 59.0% and 80.2% of excess deaths in osteosarcoma and Ewing sarcoma survivors respectively, whilst the corresponding excess SPN deaths were 34.7% and 13.1%.

There was a steep increase in mortality during the initial five years following five-year survival where the cumulative mortality reached 10.4% (95%CI:8.3-13.0) (**Figure 3.1**). Subsequently, there was a more gradual incline to 20.6% (95%CI:17.3-24.3) at 35 years post-diagnosis. When stratified by tumor type (**Figure 3.2**) a significant difference (P=0.004) in cumulative mortality was observed for recurrences, where Ewing sarcoma survivors had nearly double the cumulative mortality at 35 years post-diagnosis (osteosarcoma:8.5% vs. Ewing sarcoma:16.7%). Conversely, the cumulative mortality due to SPNs was twice as high for osteosarcoma compared to Ewing sarcoma survivors at the same point (osteosarcoma:6.7% vs. Ewing sarcoma:3.2%).

Subsequent Primary Neoplasms

Bone sarcoma survivors were 4.4-times (95%CI:3.3-5.8) more likely to experience a SPN than expected and had 29.3 (95%CI:18.7-39.9) excess SPNs per 10,000 person-years (**Table 3.3**). By SPN cancer type, survivors overall and by tumor type were at a considerably higher

risk of developing a subsequent bone neoplasm and to a lesser extent a breast neoplasm. Specifically overall, survivors were 136.3- (95%CI:79.2-234.8) and 4.5-times (95%CI:2.6-8.0) more at risk than the general population for bone and breast cancers, respectively. When the SIRs were assessed by follow-up, a 8.4-fold (95%CI:6.1-11.2) increased risk was observed during 0-24 years, where the SIR for subsequent breast and bone cancer were 10.8 (95%CI:5.2-19.9) and 154.3 (95%CI:82.2-263.8) respectively. Beyond 25 years of follow-up, the SIR for any SPN was not significantly higher in survivors than expected from the general population.

There was a continuous and steady increase in cumulative incidence for SPNs over follow-up, ultimately reaching 8.3% (95%CI:5.9-11.2) at 30 years post-diagnosis (**Figure 3.3**). When stratified by tumor type, the cumulative incidence curves were nearly identical to each other and to bone sarcoma survivors overall (P>0.05).

Questionnaire Ascertained Data

Healthcare Usage

Compared to the general population sample, bone sarcoma survivors were almost three times (OR:2.9, 95%CI:2.3-3.7) more likely to have visited an outpatient hospital department in the previous three months (**Table 3.4**). Survivors were also over twice (OR:2.4, 95%CI:1.7-3.4) more likely to be hospitalized as an inpatient during the previous year than the general population sample. When analyzed by tumor type, both osteosarcoma and Ewing sarcoma survivors had significantly higher odds of attending the hospital as an outpatient or inpatient than expected.

Psychosocial Outcomes

Bone sarcoma survivors overall were comparable to the general population sample for being ever-married, a current drinker, or consuming harmful amounts of alcohol (**Table 3.4)**. Survivors were, however, significantly less likely to be a current smoker (OR:0.6, 95%CI:0.5-0.8) and consume alcohol over recommendations (OR:0.7, 95%CI:0.5-0.9) than the general population sample. Compared to that expected, survivors performed well in obtaining educational qualifications and were 70% more likely to have obtained at least O-levels (OR:1.7, 95%CI:1.3-2.1). When analyzed by tumor type, the odds for each psychosocial outcome were comparable to the overall finding.

Health Status

Compared to the general population sample, bone sarcoma survivors overall were significantly more limited in all SF-36 scales with the exception of role-emotional (**Figure 3.4**). The most notable differences occurred in physical function, role-physical, and pain. For the individual components of the physical function scale (**Figure 3.5**), 54% and 61% of survivors were limited in "moderate activities" and "walking more than one mile" compared to the 8% and 11% expected from the general population sample respectively. In the role-physical scale (**Figure 3.6**), the largest difference between the survivors and general population sample was in "being limited in the kind of work and activities," although all component questions reported at least a 10% deficit. Finally, for the pain scale (**Figure 3.7**), survivors reported more bodily pain (12% vs. 5%) and more pain interference (16% vs. 5%) during the past four weeks compared to the general population sample.

When stratified by tumor type, osteosarcoma survivors were assessed additionally by amputation status, where only arm or leg amputations as a form of initial treatment for the first primary tumor were included. Compared to the general population sample, osteosarcoma amputee survivors reported being the most limited in all scales relative to osteosarcoma non-amputees and Ewing sarcoma survivors, with a significantly (P<0.001) higher disadvantage in physical function (**Figure 3.4**).

Discussion

This is the first large scale population-based study to provide a comprehensive description of long-term health and social outcomes among a large cohort of five-year bone sarcoma survivors, both overall and by tumor type, beyond 35-years post-diagnosis. Mortality estimates in this cohort were elevated seven-times that expected and varied significantly between tumor types, which were consistent with previous findings of a large-scale US study[2]. Past studies have also shown the principal cause-of-death was neoplastic-related[16–18]. However, to our knowledge, this is the first study that has shown substantial differences when comparing excess and cumulative mortality between tumor types; osteosarcoma survivors had double the cumulative mortality for SPNs compared to Ewing sarcoma and Ewing sarcoma survivors had double the cumulative mortality for recurrences compared to osteosarcoma at 35 years post-diagnosis. The osteosarcoma survivors in this study were much more likely to have an amputation than Ewing sarcoma, which may partially explain why osteosarcoma survivors were less likely to have recurred[19]. Additionally, due to the extended follow-up available, this is the first study to show that beyond 25 years follow-up the risk of dying from all-causes is comparable to the general population and unlikely to exceed 2.7-fold that expected. This is in contrast to dying before 25 years of follow-up, where the risk is 12.7-fold that expected. This provides important evidence for clinicians who monitor survivors treated in similar decades to those included in the BCCSS. A possible explanation for this striking absence or low risk of excess mortality with extended follow-up may relate to our previous observation that, as the overall cohort of childhood cancer survivors ages, a large proportion of excess deaths are attributed to SPNs[20], particularly breast, digestive, genitourinary, and lung carcinomas. Although carcinomas of these sites are common cancers of adulthood in the general population, in childhood cancer survivors they are principally caused by direct

radiotherapy exposure[20]. As 80% of the bone sarcomas included here were diagnosed in the limb, there is unlikely to have been much direct exposure from radiotherapy to tissues of these sites due to the lack of proximity of the radiotherapy fields.

The overall and tumor type-specific SIRs for SPNs were consistent with previous studies[3,21–23]. Additionally, our findings are consistent with previous literature in that the most common SPN was breast cancer for osteosarcoma survivors and bone cancer for Ewing sarcoma survivors[22]. Due to the extended follow-up available, this is the first study to show that the risk of developing SPNs was 9.9-fold the expected during 0-24 years follow-up and comparable to the general population beyond 25 years follow-up, where it was unlikely to exceed 2.0-fold that expected. Notably, all 13 bone cancers occurred before 25 years follow-up, nine of which developed inside or on the edge of tissue directly irradiated to treat the original bone sarcoma and one in a survivor diagnosed with a p53 mutation. This corresponds with our previous work that found that bone cancer is the most common SPN after a first primary bone sarcoma[20], which is principally attributable to exposure of the SPN site to radiation during treatment for the first cancer[24–26]. Of the two breast cancers observed subsequent to 25 years follow-up, both developed in survivors previously treated for a bone sarcoma of a lower limb with unknown p53 status.

Consistent with other studies[27–29], we reported that survivors were severely limited in health status, in particular physical function and pain. While previous studies have suggested that health status among amputees is generally similar to non-amputees[30–35], we found that osteosarcoma amputees reported the worst health status for all scales, with significantly

higher limitations in physical function relative to osteosarcoma non-amputees and Ewing sarcoma (95% of which were non-amputees) survivors.

Although we report here on appreciable proportions of the bone sarcoma survivors experiencing detrimental effects to their health, many of their social outcomes were favorable. In fact, our findings suggest that survivors were more likely than expected to obtain some types of educational qualification and less likely to be a current smoker than expected from the general population.

Current Guidelines & Recommendations

The Bone Cancer Research Trust currently recommends yearly follow-up after five-year survival[36,37]. From the evidence presented here, 74% and 21% of all excess deaths before 25 years of follow-up were due to recurrence and SPN respectively, and therefore monitoring of survivors for recurrences and SPNs, particularly during the period 5-10 years post-diagnosis where risk of recurrence is highest, could help prevent premature mortality. Bone and breast SPNs should also be a particular concern and regular follow-up should be provided, particularly in the period 0-24 years following five-year survival for bone SPNs. Factsheets given to childhood cancer survivors could further expand upon the risk of recurrence and SPNs and the potential for early diagnosis by detailing more precisely signs and symptoms relating to bone and breast neoplasms. Furthermore, the substantial excess risks of specific physical limitations and pain are likely to be useful for risk stratification and possible interventions that seek to reduce morbidity and the practical difficulties that survivors may face.

Limitations

Although the findings in this paper may not be generalizable for children diagnosed after 1991, the purpose of this study was to address the long-term, beyond 35 years post-diagnosis, outcomes that childhood bone sarcoma survivors are currently facing. We acknowledge reassessment is necessary and recommend further analyses to be conducted on the recently extended BCCSS cohort, which includes five-year survivors diagnosed from 1992-2006. Furthermore, as a large proportion of bone sarcoma diagnoses occur in individuals aged over 14 years, we recommend further analyses on adverse outcomes to be assessed using the Teenage and Young Adult Cancer Survivor Study (TYACSS), which we have established recently and includes all five-year survivors diagnosed from age 15-39 in England and Wales between 1970-2006. Finally, a potential limitation of our study is the lack of detailed treatment information. Although we report a large reduction in excess mortality and SPNs beyond 25 years follow-up, those followed-up for less than 25 years are more likely to be treated differently due to the introduction of chemotherapy. Thus, reassessment of these more recently diagnosed individuals is essential in order to determine whether the decreases in risk reported in this study remain with newer treatment practices. Nevertheless, due to our population-based design, the evidence presented here provides a reliable and unbiased basis to update clinical follow-up guidelines in relation to bone sarcoma survivors diagnosed before age 15 and treated before 1992 in Great Britain by using cancer diagnosis as a proxy.

Conclusions

In conclusion, childhood bone sarcoma survivors diagnosed between 1940 and 1991 in this cohort are at substantial risk of death and SPNs up to 25 years after five-year survival, but the risk is greatly reduced thereafter. Survivors additionally face difficulties in daily life due to their excess prevalence of poor physical health-status. As there are variations in the degree of excess depending on the specific outcome and whether they survived osteosarcoma or Ewing sarcoma, risk needs to be assessed in a stratified way. These findings should provide useful evidence for risk stratification, updating clinical follow-up guidelines, and possible intervention studies.

Characteristic	Available Survivors for Data Linkage (N=664)			Available Questionnaire Completed Survivors (N=411)		
	All N (%)	Osteosarcoma n (%)	Ewing Sarcoma n (%)	All N (%)	Osteosarcoma n (%)	Ewing Sarcoma n (%)
Sex						
Male	345 (52.0)	150 (48.5)	138 (53.1)	200 (48.7)	96 (47.8)	74 (48.1)
Female	319 (48.0)	159 (51.5)	122 (46.9)	211 (51.3)	105 (52.2)	80 (52.0)
Cancer Site						
Upper limbs	92 (13.9)	34 (11.0)	48 (18.5)	56 (13.7)	21 (10.5)	32 (20.8)
Lower limbs	436 (65.7)	262 (84.8)	132 (50.8)	273 (66.5)	170 (84.6)	75 (48.7)
Bones of skull and face	42 (6.4)	5 (1.6)	10 (3.9)	26 (6.3)	4 (2.0)	6 (3.9)
Vertebral column	24 (3.6)	3 (1.0)	15 (5.8)	13 (3.2)	3 (1.5)	7 (4.6)
Rib, sternum, clavicle	28 (4.2)	1 (0.3)	25 (9.6)	20 (4.9)	1 (0.5)	17 (11.0)
Pelvic, sacrum, coccyx	33 (5.0)	2 (0.7)	27 (10.4)	19 (4.6)	2 (1.0)	15 (9.7)
Other	9 (1.4)	2 (0.7)	3 (1.2)	4 (1.0)	0 (0)	2 (1.3)
Age at Diagnosis						
Mean (range)	10.8 (0.1-15.0)	11.5 (2.3-15.0)	10.2 (1.5-15.0)	10.8 (1.3-15.0)	11.6 (3.2-15.0)	10.0 (2.0-15.0)
0-4 years	40 (6.0)	8 (2.6)	22 (8.5)	22 (5.4)	4 (2.0)	13 (8.4)
5-9 years	185 (27.9)	74 (24.0)	84 (32.3)	122 (29.7)	46 (22.9)	58 (37.7)
10-14 years	439 (66.1)	227 (73.5)	154 (59.2)	267 (65.0)	151 (75.1)	83 (53.9)
Attained Age						
Mean (range)	39.4 (7.5-76.8)‡	40.9 (10.0-71.9)‡	35.7 (7.5-65.2)‡	43.3 (22.4-76.8)§	44.6 (22.9-71.9)§	39.4 (22.4-65.2)§
16-24 years	89 (13.4)	31 (10.0)	47 (18.1)	71 (17.3)	23 (11.4)	43 (27.9)
25-34 years	155 (23.3)	62 (20.1)	78 (30.0)	169 (41.1)	83 (41.3)	72 (46.8)
35-44 years	218 (32.8)	108 (35.0)	90 (34.6)	92 (22.4)	53 (26.4)	25 (16.2)
45+ years	202 (30.4)	108 (35.0)	45 (17.3)	79 (19.2)	42 (20.9)	14 (9.1)
Radiotherapy†						
No	201 (39.8)	150 (59.3)	17 (9.9)	125 (40.3)	98 (58.3)	10 (10.5)
Yes	304 (60.2)	103 (40.7)	154 (90.1)	185 (59.7)	70 (41.7)	85 (89.5)
Chemotherapy†						
No	195 (40.0)	93 (37.5)	40 (23.8)	109 (36.7)	58 (35.6)	16 (17.2)
Yes	292 (60.0)	155 (62.5)	128 (76.2)	188 (63.3)	105 (64.4)	77 (82.8)
Surgery†						
No	160 (31.3)	34 (13.2)	109 (63.4)	93 (29.4)	19 (11.1)	62 (64.6)
Yes	352 (68.8)	223 (86.8)	63 (36.6)	223 (70.6)	152 (88.9)	34 (35.4)
Vital Status‡						
Alive	533 (80.3)	256 (82.9)	203 (78.1)	396 (96.4)	193 (96.0)	150 (97.4)
Dead	131 (19.7)	53 (17.2)	57 (21.9)	15 (3.7)	8 (4.0)	4 (2.6)

Table 3.1: Characteristics of bone sarcoma study population overall and by tumor type

†Missing data: Radiotherapy(all data-linkage)=139, Radiotherapy(all questionnaire)=101; Chemotherapy(all data-linkage)=157, Chemotherapy(all questionnaire)=114; Surgery(all data-linkage)=152, Surgery(all questionnaire)=95

‡Age at December 31, 2010 or death/embarkation (if before December 31, 2010) – relevant to the mortality analyses

§Age at questionnaire completion – relevant to outcomes measured by the questionnaire

Underlying Cause of Death	All Bone Sarcoma Survivors										Osteosarcoma Survivors				Ewing Sarcoma Survivors				P§
	Overall				< 25 Years Follow-Up‖			≥ 25 Years Follow-Up‖			Overall				Overall				
	Person-Years	O/E	SMR (95%CI)	AER (95%CI)‡	O/E	SMR (95%CI)	AER (95%CI)‡	O/E	SMR (95%CI)	AER (95%CI)‡	Person-Years	O/E	SMR (95%CI)	AER (95%CI)‡	Person-Years	O/E	SMR (95%CI)	AER (95%CI)‡	
All Causes	15,678	131/ 18.7	7.0 (5.9,8.3)	71.6 (57.3,86.0)	115/ 9.1	12.7 (10.5,15.2)	82.7 (66.3,99.1)	16/ 9.6	1.7 (1.0,2.7)	22.3 (-5.0,49.7)	7,539	53/ 8.9	6.0 (4.5,7.8)	58.5 (39.6,77.5)	5,327	57/ 4.6	12.3 (9.4,16.0)	98.3 (70.6,126.1)	<0.001
Recurrence	15,678	80/ 0.0	NA	51.0 (39.8,62.2)	79/ 0.0	NA	61.6 (48.1,75.2)	1/ 0.0	NA	3.5 (-3.4,10.3)	7,539	26/ 0.0	NA	34.5 (21.2,47.7)	5,327	42/ 0.0	NA	78.8 (55.0,102.7)	
SPN	15,678	31/ 5.5	5.6 (3.8,8.0)	16.2 (9.3,23.2)	24/ 1.7	14.4 (9.2,21.5)	17.4 (9.9,24.9)	7/ 3.9	1.8 (0.7,3.7)	10.9 (-7.2,29.0)	7,539	18/ 2.7	6.7 (4.0,10.6)	20.3 (9.3,31.3)	5,327	8/ 1.1	7.1 (3.1,14.1)	12.9 (2.5,23.3)	0.772
Circulatory	15,678	8/ 3.6	2.3 (1.0,4.4)	2.8 (-0.7,6.4)	3/ 1.0	3.0 (0.6,8.7)	1.6 (-1.1,4.2)	5/ 2.5	2.0 (0.6,4.6)	8.6 (-6.7,23.9)	7,539	3/ 1.7	1.8 (0.4,5.3)	1.8 (-2.7,6.3)	5,327	2/ 0.7	3.0 (0.4,11.0)	2.5 (-2.7,7.7)	0.598
External	15,678	5/ 4.7	1.1 (0.3,2.5)	0.2 (-2.6,3.0)	5/ 3.9	1.3 (0.4,3.0)	0.8 (-2.6,4.3)	0/-	NP	NP	7,539	3/ 2.2	1.4 (0.3,4.0)	1.0 (-3.5,5.5)	5,327	1/ 1.6	0.6 (0.0,3.6)	-1.0 (-4.7,2.6)	0.535

Table 3.2: All cause and cause-specific† standardized mortality ratios and absolute excess risk for bone sarcoma survivors within the British Childhood Cancer Survivor Study (BCCSS) overall and by tumor type

SMRs and AERs where there are less than 5 observed events should be interpreted with caution

Abbreviations: O-observed number, E-expected number, CI-confidence intervals, SMR-standardized mortality ratios, AER-absolute excess risk, NA-not applicable, NP-not possible to reliably calculate due to very small expected number

†Results are only reported for underlying causes-of-deaths with at least five observed events overall. Other causes-of-death were: 4 genitourinary, 1 digestive, 1 infection, 1 unknown

‡Per 10,000 person-years

§Comparing SMRs for osteosarcoma and Ewing sarcoma survivors for

‖From five-year survival

SPN	All Bone Sarcoma Survivors									Osteosarcoma Survivors			Ewing Sarcoma Survivors			P§
	Overall			< 25 Years Follow-Up‖			≥ 25 Years Follow-Up‖			Overall			Overall			
	O/E	SIR (95% CI)	AER (95% CI)†	O/E	SIR (95% CI)	AER (95% CI)‡	O/E	SIR (95% CI)	AER (95% CI)‡	O/E	SIR (95% CI)	AER (95% CI)‡	O/E	SIR (95% CI)	AER (95% CI)‡	
Any Cancer Site	49/11.2	4.4 (3.3,5.8)	29.3 (18.7, 39.9)	44/5.3	8.4 (6.1,11.2)	34.7 (23.1,46.3)	5/5.9	0.8 (0.3,2.0)	-5.1 (-30.2,20.0)	23/6.0	3.9 (2.6,5.8)	26.1 (11.7,40.5)	19/2.8	6.7 (5.3,10.6)	35.7 (16.9,54.6)	0.070
Breast	12/2.6	4.5 (2.6,8.0)	7.2 (2.0,12.5)	10/0.9	10.8 (5.2,19.9)	8.1 (2.6,13.7)	2/1.7	1.2 (0.1,4.2)	1.6 (-14.2,17.5)	6/1.5	4.0 (1.8,8.8)	6.9 (-0.5,14.2)	5/0.6	7.8 (3.2,18.6)	9.6 (-0.1,19.3)	0.236
Bone	13/0.1	136.3 (79.2,234.8)	10.0 (4.5,15.5)	13/0.1	154.3 (82.2,263.8)	11.6 (5.2,17.9)	0/-	NP	NP	3/0.05	65.4 (21.1,202.7)	4.5 (-0.7,9.7)	8/0.04	223.0 (111.5,445.9)	17.6 (5.4,29.8)	0.057

Table 3.3: Overall and site-specific† standardized incidence ratios and absolute excess risks of second primary neoplasms for bone sarcoma survivors within the British Childhood Cancer Survivor Study (BCCSS)
SIRs and AERs where there are less than 5 observed events should be interpreted with caution
Abbreviations: O-observed number, E-expected number, CI-confidence intervals, SIR-standardized incidence ratios, AER-absolute excess risk, NA-not applicable, NP-not possible to reliably calculate due to very small expected number
†Results are only reported for site-specific SPNs with at least five observed events overall. Other SPNs were: 4 genitourinary, 4 bladder, 3 digestive, 3 connective and soft tissue, 3 malignant neoplasms with unspecified sites, 2 gliomas, 2 Hodgkin lymphoma, 2 NHL, 2 leukemia, 1 respiratory, 1 eye, 1 thyroid
‡AER is shown per 10,000 person-years
§Comparing SIRs for Osteosarcoma and Ewing Sarcoma survivors
‖From five-year survival

	UK Norms (ref)	Bone Sarcoma Overall OR (95%CI)	Osteosarcoma OR (95%CI)	Ewing Sarcoma OR (95%CI)
Marital Status†				
Males Ever-married	1.0	0.7 (0.5,1.0)	1.0 (0.6,1.6)	0.7 (0.4,1.3)
Females Ever-married	1.0	0.8 (0.6,1.1)	0.8 (0.5,1.2)	0.9 (0.6,1.4)
Education‡				
University degree or higher	1.0	1.2 (1.0,1.6)	1.5 (1.1,2.1)	1.0 (0.8,1.5)
Teaching qualification or higher	1.0	1.1 (0.9,1.4)	1.3 (1.0,1.7)	1.0 (0.7,1.4)
A-levels or higher	1.0	1.2 (1.0,1.5)	1.2 (0.9,1.6)	1.1 (0.8,1.5)
O-levels or higher	1.0	1.7 (1.3,2.1)	1.8 (1.2,2.6)	2.0 (1.2,3.1)
Alcohol§				
Current drinker	1.0	0.8 (0.6,1.1)	1.0 (0.6,1.6)	0.8 (0.5,1.3)
Consuming over recommendations	1.0	0.7 (0.5,0.9)	0.7 (0.5,1.1)	0.5 (0.3,0.9)
Consuming harmful amounts	1.0	0.7 (0.4,1.1)	0.6 (0.3,1.4)	0.7 (0.3,1.5)
Smoking§				
Current smoker	1.0	0.6 (0.5,0.8)	0.7 (0.5,1.0)	0.6 (0.4,0.9)
Use of Health Services‖				
Talked to a doctor¶	1.0	1.2 (0.9,1.6)	1.3 (0.9,1.8)	1.2 (0.8,1.8)
Attended as outpatient¶	1.0	2.9 (2.3,3.7)	2.9 (2.1,4.0)	3.2 (2.2,4.7)
Attended as day patient*	1.0	1.1 (0.7,1.5)	1.2 (0.7,1.9)	1.0 (0.6,1.8)
Attended as inpatient*	1.0	2.4 (1.7,3.4)	2.5 (1.6,3.9)	2.8 (1.7,4.7)

Table 3.4: Percentages and odds ratios (with corresponding 95% confidence intervals) for the likelihood of use of health services and psychosocial outcomes in bone sarcoma survivors within the British Childhood Cancer Survivor Study (BCCSS) compared with the general population of Britain

Abbreviations: OR-odds ratio, CI-confidence interval

†From a pooled Mantel Haenszel model controlling for attained age

‡From a GEE multivariate logistic regression controlling for age at questionnaire completion and sex (taking into account the GHS weighting factor)

§From a GEE multivariate logistic model adjusting for attained age (≤69 years), sex, marital status, socioeconomic classification, educational attainment, and region (taking into account the GHS weighting factor)

‖From a GEE multivariate logistic model adjusting for age at questionnaire completion, sex, and educational attainment

¶Excluding women who were pregnant at time of survey

*Excluding visits for having a baby

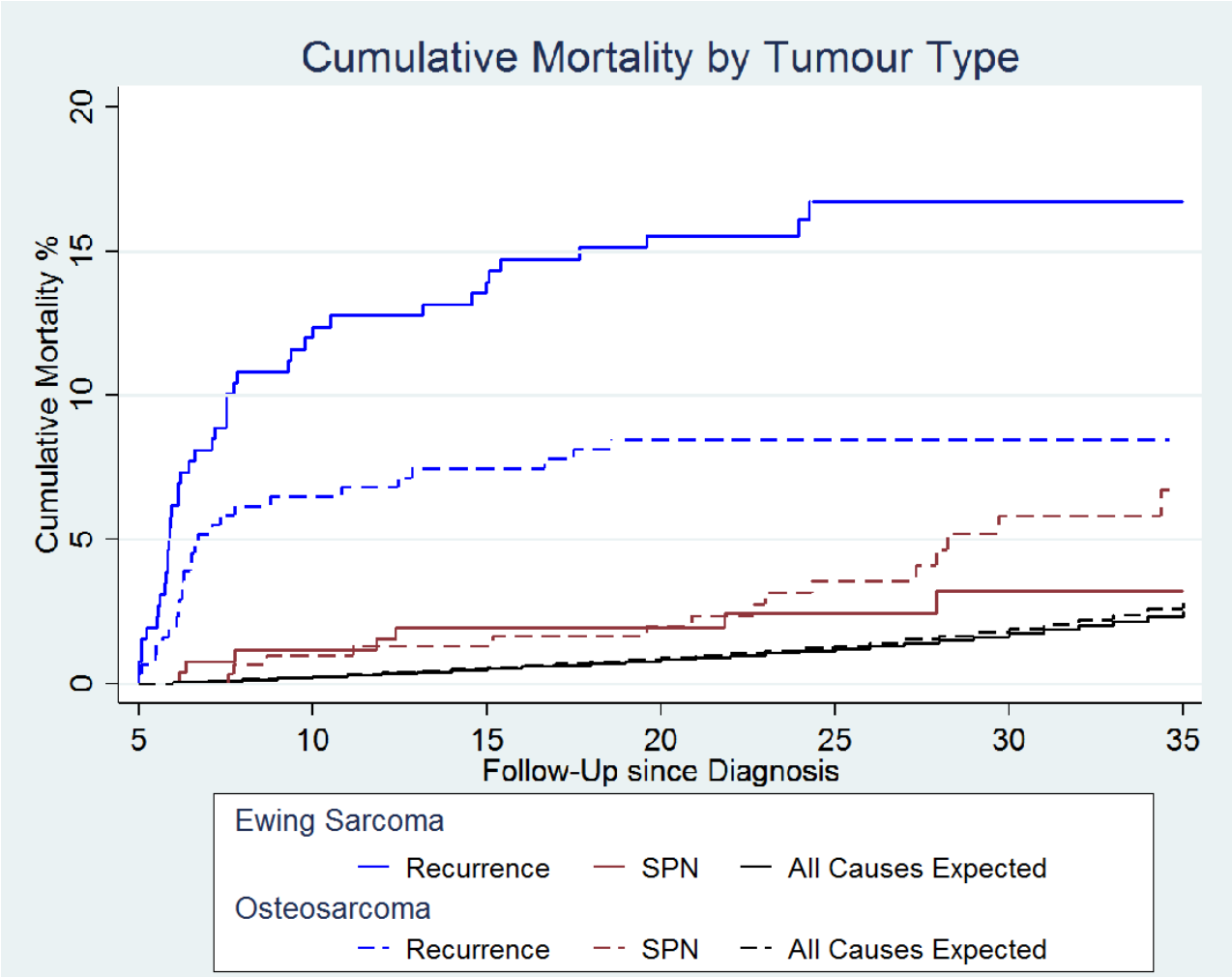

Figure 3.1: Cumulative mortality of recurrence and second primary neoplasms among childhood bone sarcoma survivors within the British Childhood Cancer Survivor Study (BCCSS) by tumor type

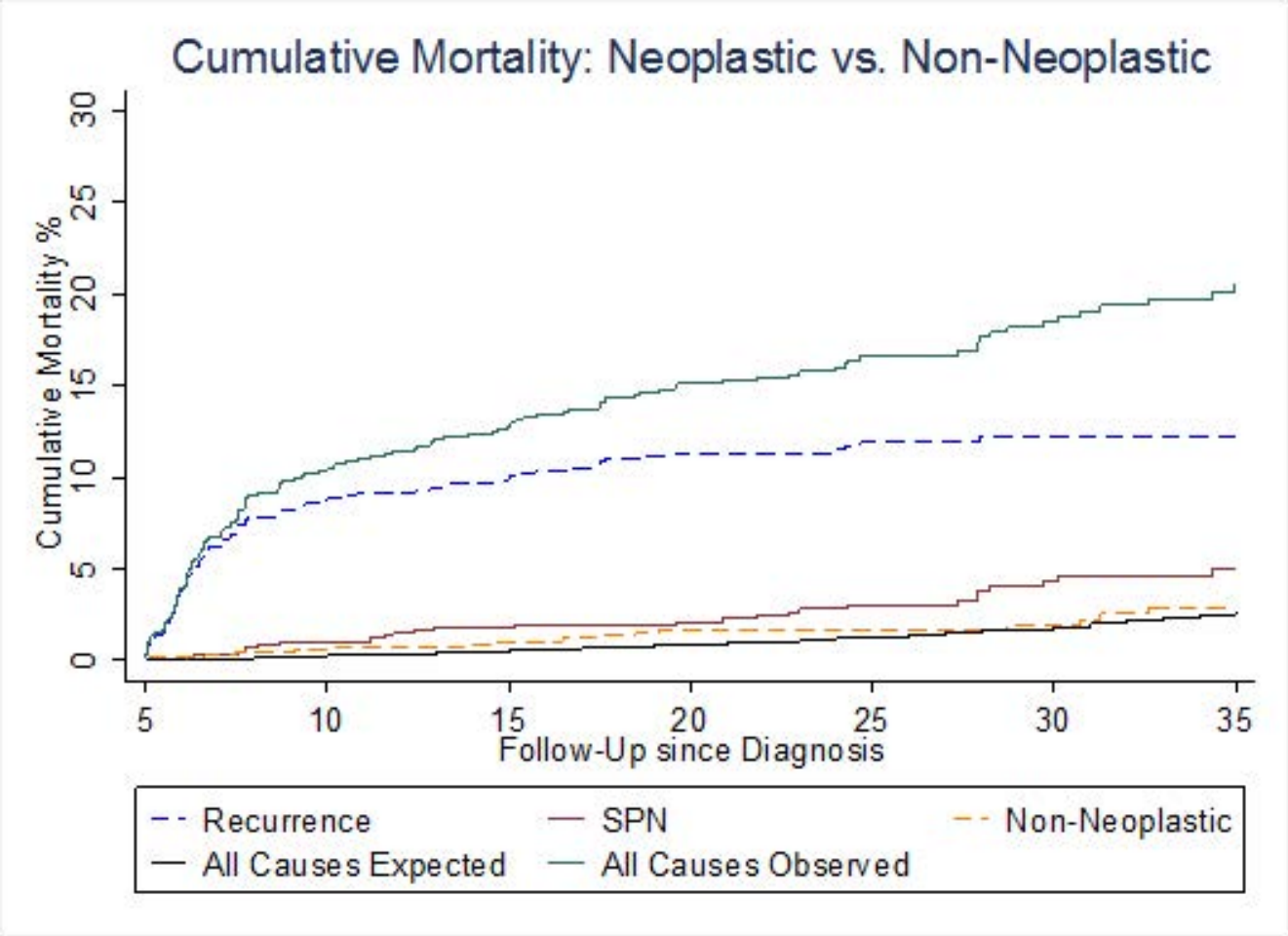

Figure 3.2: Cumulative mortality of neoplastic versus non-neoplastic causes-of-death among childhood bone sarcoma survivors within the British Childhood Cancer Survivor Study (BCCSS)

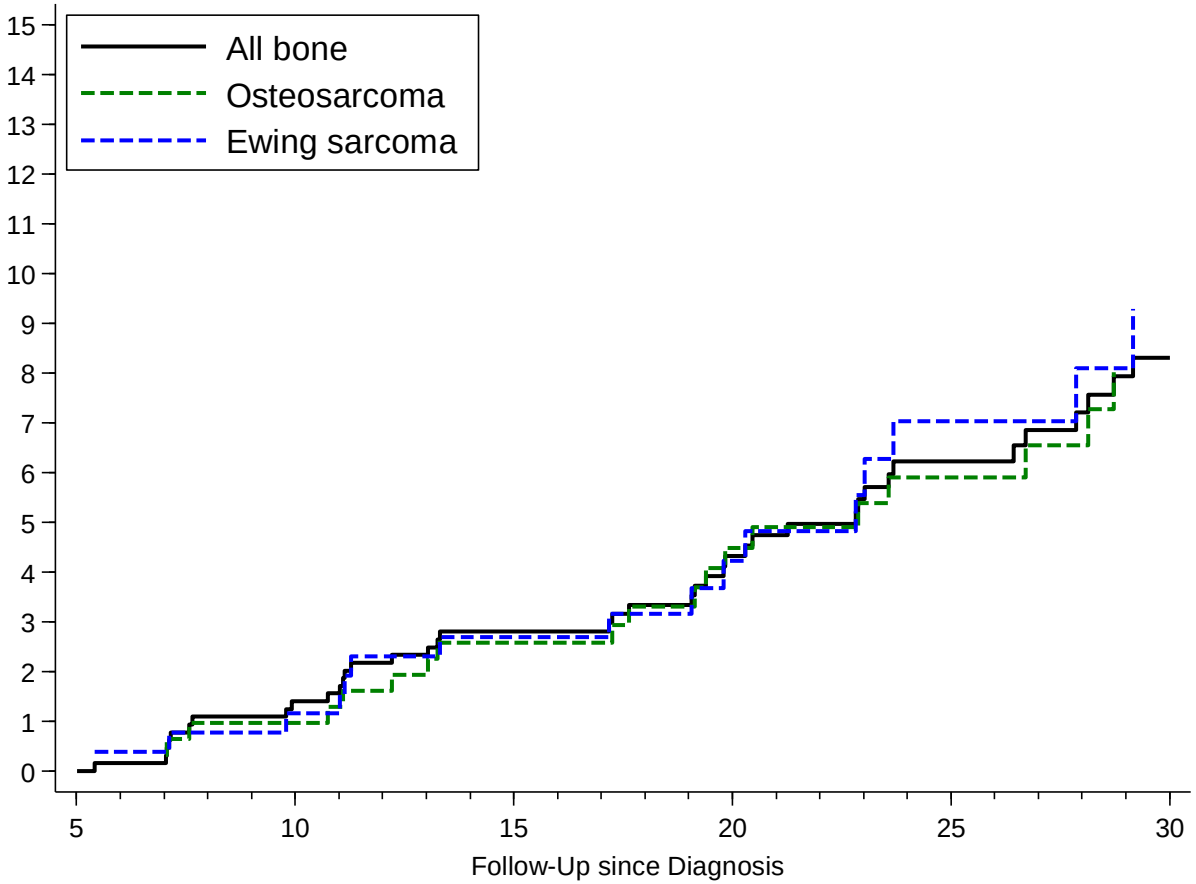

Figure 3.3: Observed cumulative incidence of a subsequent primary neoplasm among bone sarcoma survivors within the British Childhood Cancer Survivor Study (BCCSS) overall and by tumor type

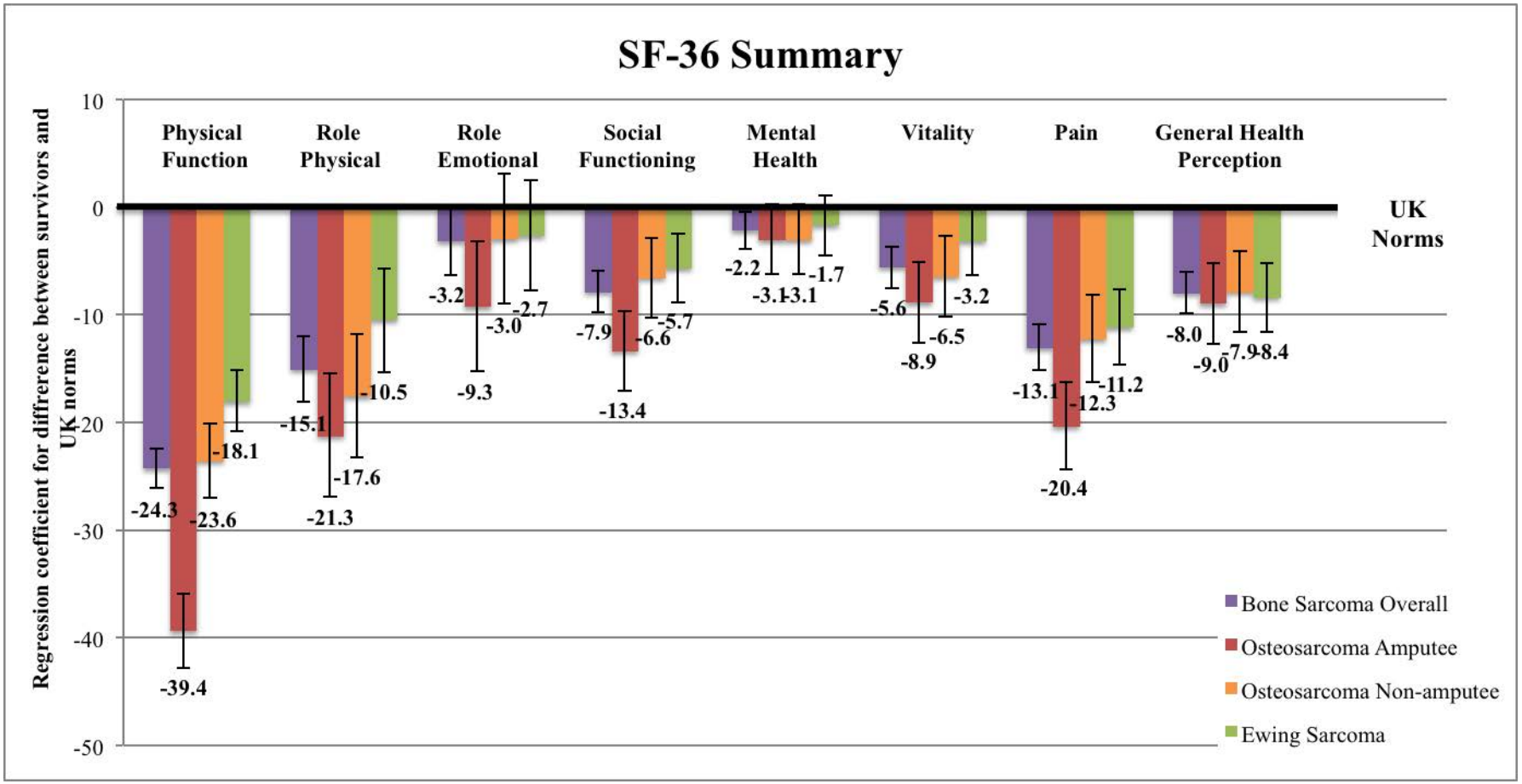

Figure 3.4: Sex and age adjusted regression coefficients and corresponding 95% confidence intervals for differences in SF-36 health status scales between bone sarcoma, osteosarcoma amputees, osteosarcoma non-amputees, and Ewing sarcoma survivors versus UK norms

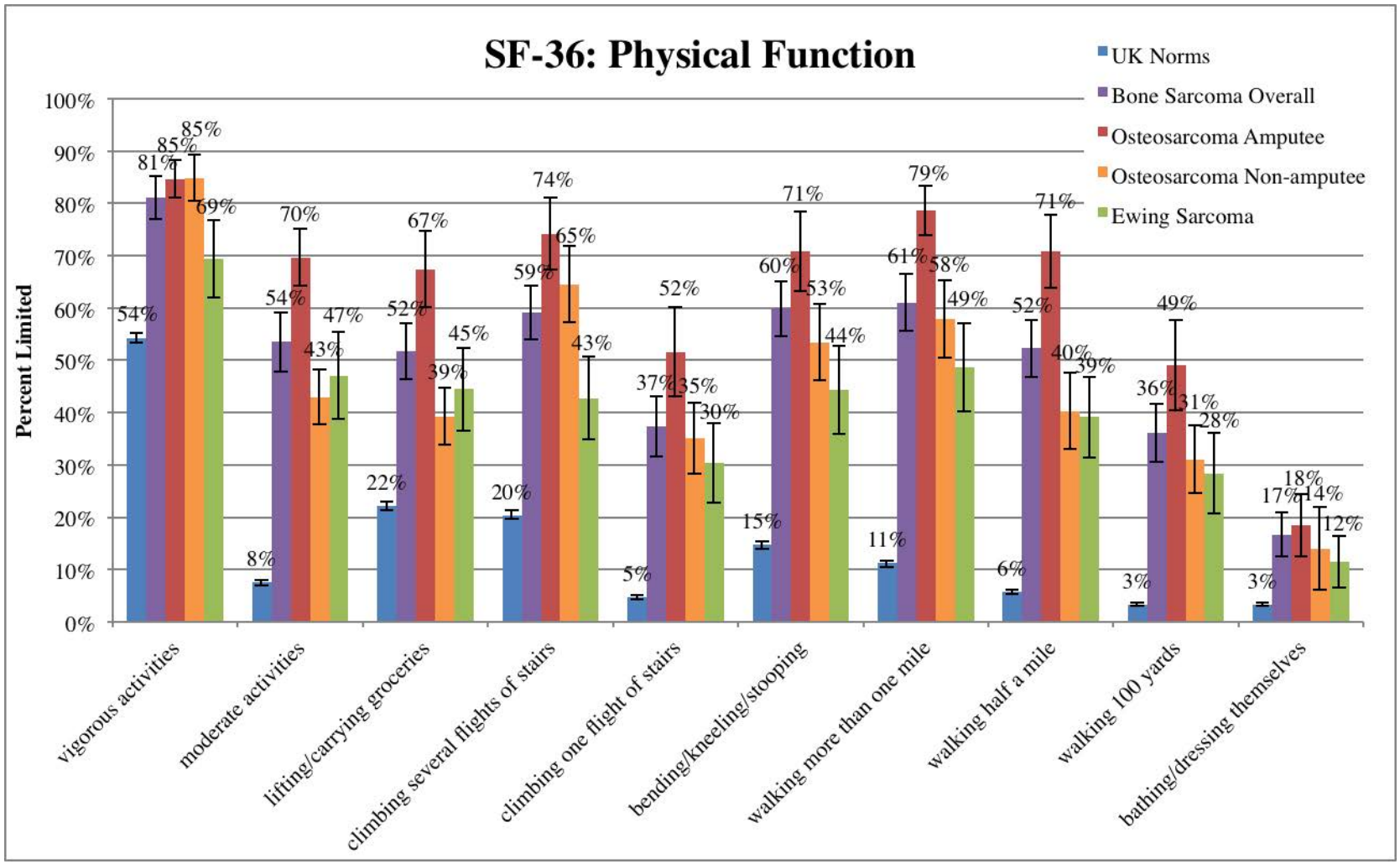

Figure 3.5: Directly (age and sex) standardized prevalence and corresponding 95% confidence intervals, of reporting being limited† in specific daily activity or other problem related to physical function score of SF-36

†Limited defined as reporting "yes, limited a lot" or "yes, limited a little" for relevant question of BCCSS questionnaire

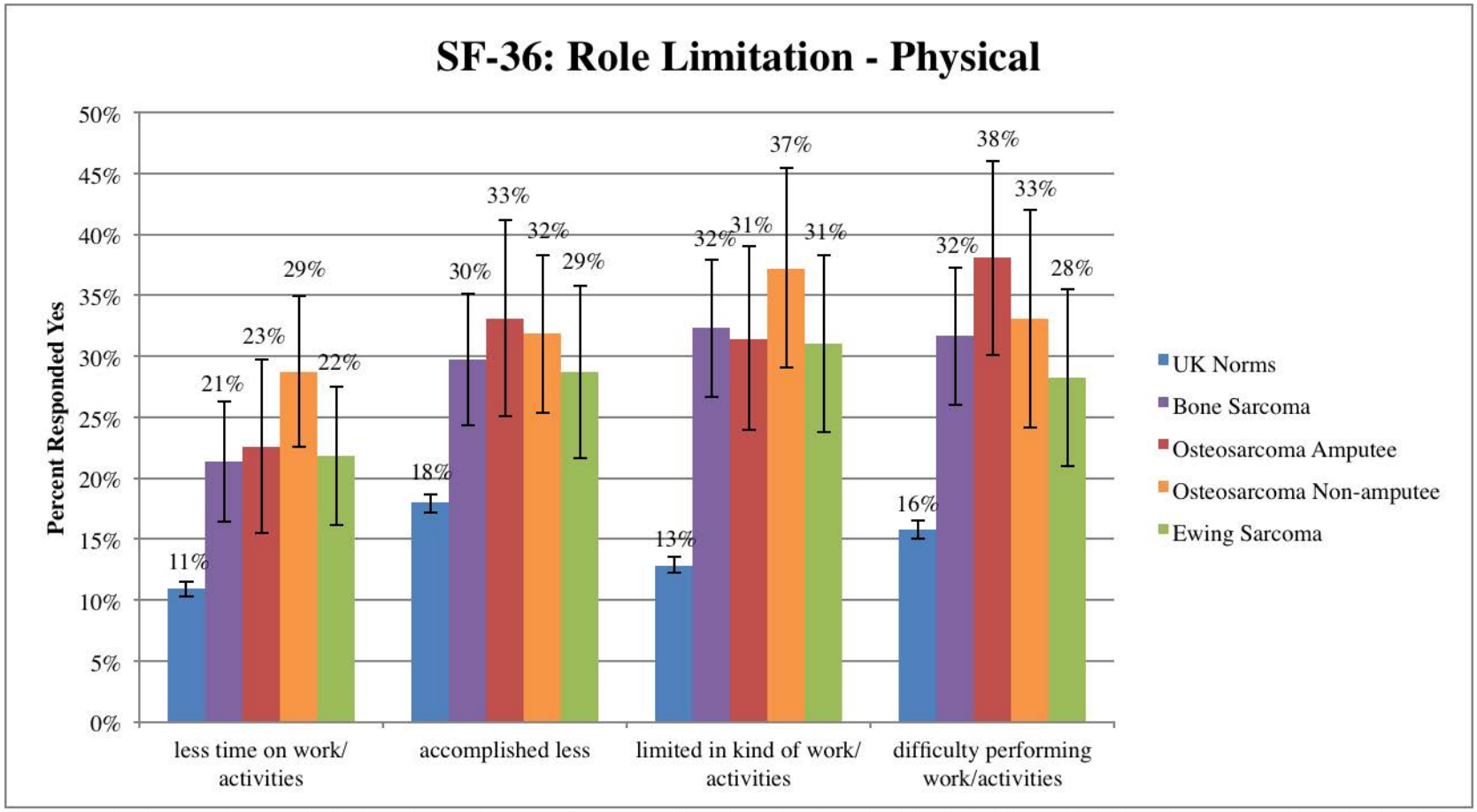

Figure 3.6: Directly (age and sex) standardized prevalence and corresponding 95% confidence intervals, of reporting being limited† in specific daily activity or other problem related to role limitation physical score of SF-36

†Limited defined as reporting "yes" for relevant question of BCCSS questionnaire

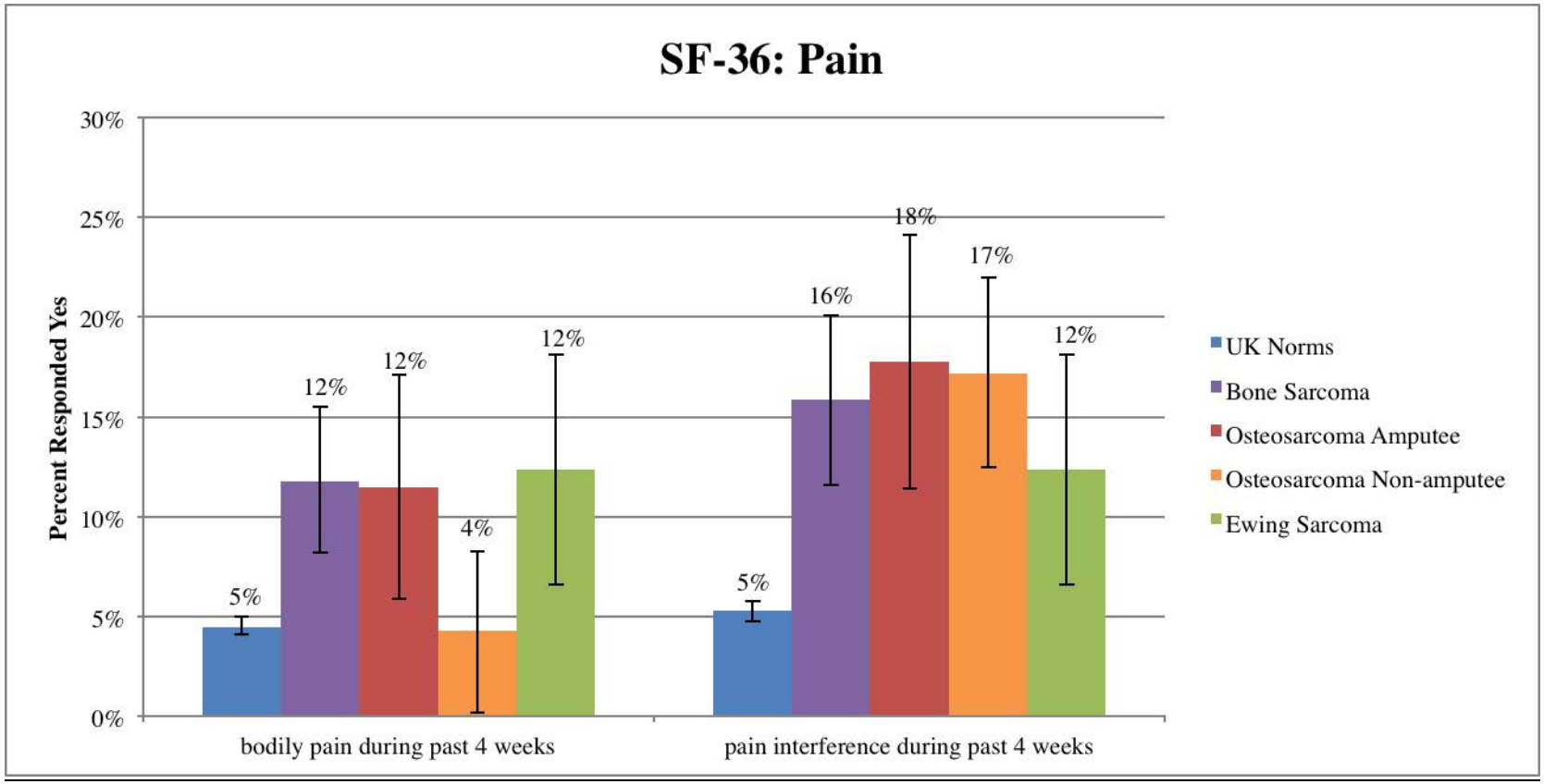

Figure 3.7: Directly (age and sex) standardized prevalence and corresponding 95% confidence intervals, of reporting being limited† in specific daily activity or other problem related to pain score of SF-36

†Limited defined as reporting "severe/very severe" or "quite a bit/ extremely" for relevant question of BCCSS questionnaire

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CHAPTER 4

STUDY 2:

Aspects of mental health dysfunction among survivors of childhood cancer

Abstract

Purpose: Some previous studies have reported that survivors of childhood cancer are at an increased risk of developing long-term mental health morbidity, whilst others have reported that this is not the case. Therefore, we analyzed five-year survivors of childhood cancer using the British Childhood Cancer Survivor Study (BCCSS) to determine the risks of aspects of long-term mental health dysfunction.

Material and Methods: Within the BCCSS, 10,488 survivors completed a questionnaire that ascertained mental health-related information via ten questions from the Short From-36 survey. Internal analyses were conducted using multivariate logistic regression to determine risk factors for mental health dysfunction. External analyses were undertaken using direct standardization to compare mental health dysfunction in survivors to UK norms.

Results: This study has shown that overall, childhood cancer survivors had a significantly higher prevalence of mental health dysfunction for 6/10 questions analyzed compared to UK norms. CNS and bone sarcoma survivors reported the greatest dysfunction, compared to expected, with significant excess dysfunction in nine and six questions, respectively; the excess ranged from 4.4%-22.3% in CNS survivors and 6.9%-15.9% in bone sarcoma survivors. Compared to expected, excess mental health dysfunction increased with attained age; this increase was greatest for reporting "limitations in social activities due to health," where the excess rose from 4.5% to 12.8% in those aged 16-24 and 45+, respectively. Within the internal analyses, higher levels of educational attainment and socioeconomic classification were protective against mental health dysfunction.

Conclusions: Based on the findings of this large population-based study, childhood cancer survivors report significantly higher levels of mental health dysfunction than those in the general population, where deficits were observed particularly among CNS and bone sarcoma survivors. Limitations were also observed to increase with age, and thus it is important to emphasize the need for mental health evaluation and services across the entire lifespan. There is evidence that low educational attainment and being unemployed or having never worked adversely impacts long-term mental health. These findings provide an evidence base for risk stratification and planning interventions.

Introduction

Although five-year survival from childhood cancer has risen substantially to approximately 80%[1], long-term survival is accompanied by an excess risk of adverse outcomes due to late effects of the cancer and its treatment. Consequently, as the number of survivors increases, it becomes ever more important to investigate the risk of such adverse effects in order to identify vulnerable subgroups. While previous studies have investigated health status among childhood cancer survivors, mental health sequelae remains a concern as psychological limitations or distress have been reported in both adolescent and adult survivors of childhood cancer[2–5]. Additionally, conflicting findings on mental health have been reported[5,6]. By identifying survivors at risk for mental health dysfunction, appropriate monitoring and early interventions within long-term care can be undertaken through risk stratification to ensure that young people and adults achieve the best possible outcomes in terms of health and social welfare, whilst optimizing the expenditure of limited resources.

The goal of this study was to investigate specific aspects of mental health dysfunction among childhood cancer survivors diagnosed between the ages of 0-14 years within the British Childhood Cancer Survivor Study (BCCSS) by assessing responses to specific questions within the Short Form-36 (SF-36) survey. Although studies have assessed aspects of mental health using this survey previously[5–10], this is the first study to our knowledge to comprehensively analyze the ten questions comprising the role-emotional, social functioning, and mental health scales, which have been shown to be the most valid among the scales as mental health measures[11,12]. By looking at specific questions, one can better determine the effect of various aspects of mental health dysfunction, which may have been previously undetected in a composite score or individual scale. The potential impact of demographic,

cancer, treatment, social, and economic explanatory factors on mental health were explored and external analyses comparing survivors to general population norms were conducted. In doing so, this large, population-based study provides further evidence on mental health morbidity among childhood cancer survivors, which may have important implications for clinicians, family members, and survivors with regard to minimizing mental health adverse late effects.

Material and Methods

Study Population

The BCCSS is a population-based cohort of 17,980 individuals diagnosed with cancer before the age of 15, between 1940-1991 in Great Britain, and who have survived at least five years[13]. The cohort was ascertained through the National Registry of Childhood Tumours, which has a high estimated level of completeness (~99%)[14]. Ethical approval for the study was obtained from a Multi-Centre Research Ethics Committee and every Local Research Ethics Committee in Britain (N = 212 in total).

Short Form-36 Survey

It was important to measure both health and social impacts on quality-of-life to understand the effect of childhood cancer treatment on long-term mental health. In order to ascertain health and social outcomes, a questionnaire was sent to all survivors in the BCCSS cohort who were alive and aged at least 16 years. Of the 14,836 survivors who were eligible to receive the questionnaire, 10,488 (70.7%) completed the survey[13]. Included in the questionnaire was the SF-36, which is a generic health survey that contains 36 questions, which measure eight dimensions of health status. From our previous work, which studied the psychometric properties of the SF-36 in the BCCSS population, we know that this survey exhibits good validity and reliability when used in long-term survivors of childhood cancer[15].

Using the available information from the SF-36, we assessed specific aspects of mental health dysfunction, henceforth only referred to as mental health dysfunction, by looking at the ten individual questions that comprise the role-emotional, social functioning, and mental health scales[11,12]. In order to assess mental health dysfunction from the responses to each question,

we dichotomized the responses (**Figure 4.1**). For the mental health scale (questions 9b, 9c, 9d, 9f, 9h) and one question relating to social functioning (question 9j), we dichotomized the responses based upon whether the sentence was positively or negatively worded, where survivors were considered to be reporting dysfunction if they answered 'all,' 'most,' 'a good bit,' or 'some' of the time to the negatively worded questions and 'some,' 'a little,' or 'none of the time' to the positively worded questions. The second social functioning question (question 6), which assessed physical or emotional interference in normal social activities, was dichotomized by categorizing responses of 'not at all' or 'slightly' as not reporting dysfunction and responses of 'moderately,' 'quite a bit,' or 'extremely' as reporting dysfunction. For the role-emotional scale (questions 5a, 5b, 5c), survivors who reported 'yes' were considered to be reporting mental health dysfunction. These dichotomized groupings were utilized in order to avoid the problems associated with having almost all survivors occupying one level of the dichotomy for responses to any question.

Comparison Group

In order to compare responses to the ten questions between survivors and the general population, the SF-36 responses from the Oxford Healthy Life Survey (OHLS) served as the reference general population sample[16,17]. The OHLS was conducted contemporaneously with the BCCSS and included 13,042 individuals aged 18-64 who were randomly sampled from the Family Health Services Authority registers for Berkshire, Buckinghamshire, Northamptonshire and Oxfordshire. The OHLS sample resembles the UK general population with regard to socio-demographic characteristics[17], and the characteristics of the OHLS have been compared to BCCSS survivors previously with only slight differences being observed[6].

OHLS responses to the SF-36 were dichotomized as described above so that responses from survivors and the general population sample were treated identically.

Statistical Analyses – Internal Comparison

Internal analyses, using multivariate logistic regression, were conducted in order to determine risk factors for mental health dysfunction among five-year childhood cancer survivors within each of the ten questions. All models adjusted for the following factors: age at diagnosis, sex, first primary neoplasm (FPN) diagnosis, age at questionnaire completion, marital status, socioeconomic classification (SEC), and educational attainment. We decided a priori to use leukemia survivors as the referent group because previously published literature on health status has been conducted in this manner[18]. Odds ratios (ORs) and 95% confidence intervals (CIs) were reported. Likelihood ratio tests were used to assess the significance of fitted models and trends.

Statistical Analyses – External Comparison

In order to compare the prevalence of mental health dysfunction between survivors and the general population, external analyses were completed using direct (age and sex) standardization. For these analyses, the general population sample acted as the reference group and survivors were compared overall and separately by FPN diagnosis and attained age. Prevalence of mental health dysfunction was reported as percentages with corresponding 95% CIs.

All analyses were undertaken using Stata 12.1[19]. Statistical significance was defined as a two-sided *P*-value less than 0.05.

Results

Study Characteristics

Survivors who were female, treated for a FPN of a central nervous system (CNS) tumor, unemployed or having never worked, or educationally unqualified were found to consistently report the highest prevalence of dysfunction across all ten questions (**Table 4.1**). Survivors who were separated, divorced, or widowed also generally reported more dysfunction than those who were single, cohabiting, or married. Mental health dysfunction within the ten questions did not appear to differ substantially by age at diagnosis, treatment modalities (radiotherapy, chemotherapy, surgery), or age at questionnaire completion.

Internal Comparison

Risk factors associated with reporting mental health dysfunction within the role-emotional scale

Table 4.2 presents the multivariate models for the three mental health questions within the role-emotional scale. Females were significantly more likely to be limited in all three questions (*P*heterogeneity<0.0001). Across FPN diagnoses there were statistically significant heterogeneity for all three questions where, compared to leukemia survivors, survivors of non-Hodgkin lymphoma (NHL), CNS tumors, and bone sarcoma were significantly more likely to be limited for all questions (*P*heterogeneity<0.05). Also, compared to leukemia survivors, heritable retinoblastoma survivors reported significantly more mental health dysfunction in "the amount of time spent on work/activities" (OR:1.7,95%CI:1.1-2.4) and "accomplishing as much as desired" (OR:1.7,95%CI:1.2-2.3), whereas Hodgkin lymphoma (HL) survivors reported significantly more dysfunction in "doing work or other activities as carefully as usual" (OR:1.4,95%CI:1.0-1.8). Compared to individuals aged 16-24 at

questionnaire completion, the risk for reporting mental health dysfunction in all three questions increased linearly with age (*P*trend<0.005). An analysis by marital status showed for all three questions that, relative to single survivors, those who were separated were most at risk of reporting dysfunction, whereas those who were married were significantly less likely to report dysfunction. An association was found for educational attainment, where increased qualifications were associated with decreased odds of reporting dysfunction in all three questions. For all three questions, relative to students, survivors who had never worked or were unemployed were significantly more likely to report mental health dysfunction, whereas those who were in managerial or professional positions were significantly less likely to report dysfunction.

Risk factors associated with reporting mental health dysfunction within the social functioning scale

In the multivariate models assessing the two questions within the social functioning scale, females were again significantly more likely to report dysfunction compared to males (**Table 4.3**). An analysis by FPN diagnosis showed that compared to those diagnosed with leukemia, CNS (OR:1.6,95%CI:1.4-1.9), neuroblastoma (OR:1.5,95%CI:1.1-2.0), bone sarcoma (OR:2.0,95%CI:1.5-2.7), and soft tissue sarcoma (STS) (OR:1.3,95%CI:1.0-1.7) survivors were all significantly more likely to report mental health dysfunction due to "physical health or emotional problems interfering with normal activities." NHL, CNS, neuroblastoma, heritable retinoblastoma, bone sarcoma, and STS survivors also reported significantly higher dysfunction in "social activities due to their health", compared to leukemia survivors, with bone sarcoma (OR:3.0,95%CI:2.3-4.0) and CNS survivors (OR:2.5,95%CI:2.1-2.9) being the most limited. Age at questionnaire completion was significantly associated with reporting

dysfunction in both questions where those aged 25-34, 35-44, and 45+ reported more dysfunction compared to those aged 16-24 (*P*trend<0.0001). Relative to single survivors, married survivors were significantly less likely to report dysfunction in either question (*P*heterogeneity<0.001); no significant difference was found between single survivors and those who were cohabiting, separated, divorced, or widowed. An analysis by educational attainment showed that, compared to survivors with no qualifications, the odds of reporting mental health dysfunction decreased with higher levels of qualifications for both questions. SEC was also found to be significantly related to reporting dysfunction in both questions where, compared to students, those who never worked or were unemployed were significantly more likely report dysfunction (*P*heterogeneity<0.001) and those in managerial or professional positions were significantly less likely to report dysfunction (*P*heterogeneity<0.001).

Risk factors associated with reporting mental health dysfunction within the mental health scale

Survivors who were female or who had never worked or were unemployed were significantly more likely to report mental health dysfunction in all five questions within in the mental health scale relative to males and students, respectively (**Table 4.4**). Conversely, survivors who achieved an O-level, A-level, teaching qualification, or degree were significantly less likely to report dysfunction in all questions compared to students. Age at questionnaire completion was also found to be significantly associated with reporting dysfunction in 4/5 questions, but a consistent trend was not observed within the subgroups compared to those aged 16-24. When analyzed by marital status, survivors who were married were found to report significantly less mental health dysfunction in 4/5 of the questions, compared to those

who were single. Survivors who were cohabiting also reported significantly less mental health dysfunction for the question relating to "being a very nervous person" (OR:0.8,95%CI:0.7-1.0). Survivors who were separated, conversely, reported a 70% increase in mental health dysfunction compared to single survivors (OR:1.7,95%CI:1.2-2.4). When asked if the survivor had "been a very nervous person", those diagnosed with CNS (OR:1.3,95%CI:1.1-1.5), compared to leukemia, were significantly more likely to agree with this statement. Furthermore, in the multivariate model assessing whether survivors have "been a happy person", an analysis by FPN diagnosis showed that HL (OR:1.3,95%CI:1.0-1.6), NHL (OR:1.4,95%CI:1.1-1.8), CNS (OR:1.4,95%CI:1.2-1.6), neuroblastoma (OR:1.3,95%CI:1.0-1.7), non-heritable retinoblastoma (OR:1.4,95%CI:1.0-1.8), and bone sarcoma (OR:1.5,95%CI:1.1-1.9) survivors reported significantly higher dysfunction compared to leukemia survivors.

External Comparison

Compared to the general population sample, survivors overall reported more mental health dysfunction in 6/10 questions that were examined (**Table 4.5**). When further assessed by FPN diagnosis, CNS and bone sarcoma survivors were found to report the greatest dysfunction, compared to that expected, with significant differences in ten and six questions, respectively; the excess of dysfunction ranged from 4.4%-22.3% in CNS survivors, whereas bone sarcoma survivors were limited from 6.9%-15.9%. Both diagnostic groups were most disadvantaged by their health limiting their social activities. Conversely, survivors of neuroblastoma, heritable retinoblastoma, non-heritable retinoblastoma, Wilms, and other (those that did not conform to one of the ten FPN groups used) were not significantly different in any of the questions analyzed when compared to the general population sample.

An analysis by age at questionnaire completion showed that the prevalence of mental health dysfunction was comparable or better for 7/10 questions among survivors aged 16-24, compared to that expected from the general population sample (**Table 4.6**); survivors in this age group did however report a higher prevalence of "being a nervous person" (30.7% vs. 23.7% expected) "feeling down in the dumps" (25.3% vs. 21.2% expected) and "being limited in their social activities due to their health" (15.7% vs. 11.2% expected). Among those aged 25-34 and 35-44 at questionnaire completion, significantly higher mental health dysfunction was reported, compared to the general population sample, in relation to 6 questions (questions 5a, 6, 9b, 9c, 9f, 9j). Similarly, survivors aged 45 and older reported significantly higher dysfunction in 5 questions compared to that expected. Notably, the percent difference in mental health dysfunction between survivors and the general population increased with age at questionnaire completion for both questions from the social functioning scale and the question relating to "feeling downhearted and low"; this increase was most noticeable among those reporting "limitations in social activities due to their health", where the excess rose from 4.5% to 12.8% in those aged 16-24 and 45+, respectively. Statistically significant variation in the excess by age at questionnaire completion was not observed in four questions, which related to problems with work or daily activities and feeling calm, peaceful, or happy.

Discussion

The findings from this large population-based study indicate that the prevalence of mental health dysfunction among survivors of childhood cancer in the BCCSS was substantially higher than that expected from the general population sample in over half of the questions assessed, with survivors of CNS and bone sarcoma being the most vulnerable; these findings are generally consistent with other studies that have used the SF-36[7] or similar psychological measures[5,18,20], although some studies have suggested that mental health status was similar between survivors and comparative populations[5,6,21]. While the North American Childhood Cancer Survivor Study (CCSS) found significantly higher limitations in the role-emotional and social functioning scales for survivors overall, survivors of CNS and bone sarcoma were reported as having significantly less problems on the mental health scale compared to that expected from the US population reference[10]; this finding does not correspond with our results as CNS and bone sarcoma survivors were found to be significantly more limited in 5/5 and 3/5 of the questions that comprise the mental health scale, respectively. The same study[10] also reported significantly higher limitations in regards to the role-emotional and social functioning scales for HL, NHL, Wilms, and neuroblastoma survivors, compared to US norms, which conflicts with the results presented in this study as these survivors were not significantly more limited in any of the questions comprising these scales compared to the general population sample. These inconsistencies with our study might reflect differences in study demographics, cohort design, or therapeutic practice between North America and Great Britain.

Another important finding in this study was that, although younger survivors (16-24 years) perceived their mental health as broadly similar to the general population, significant mental

health dysfunction was reported in at least half of the questions among those aged 25 years and older. A particular concern was found among the questions relating to social functioning as significant mental health dysfunction was reported for all age groups. Furthermore, the extent of the excess among survivors increased with age at questionnaire completion for both questions within the social functioning scale. This finding corresponds with another study that reported significantly more disadvantage in the social functioning scale in those assessed 10-14 and 15-19 years from diagnosis compared to a control group[7]. A possible explanation as to why mental health dysfunction increased with age may be due to the fact that the risk of complex and multiple late effects emerging increases as time since treatment increases[22–25]. Although late effects may not immediately affect survivors, they may become more important with maturity and influence life decisions and experiences later on. For example, infertility may become a greater concern and impact mental health when survivors want to start a family. Living with chronic health conditions, such as infertility, cardiovascular disease, diabetes, blindness, physical disability, and epilepsy, which can often be managed but not cured, may have long-term consequences on both physical and psychological health, stressing the importance for life course care and services.

The internal analyses similarly revealed that CNS and bone sarcoma survivors reported higher levels of mental health dysfunction compared to other types of childhood cancer, with CNS survivors being limited in all questions assessed and bone sarcoma survivors being limited in all questions relating to the social functioning and role-emotional scales. Broadly, this finding conflicts with an analysis by the CCSS, which found no significant difference among childhood cancer survivors by FPN diagnosis[18]; however, it is worth noting that in the CCSS the Brief Symptom Inventory 18 survey was used and thus results are not directly

comparable. Other risk factors for mental health dysfunction included being female, separated from a spouse/partner, and unemployed or having never worked, which corresponds with previous reports using the SF-36[5,10] or similar measures to predict psychological distress[18]. Low educational attainment, unemployment, and other socioeconomic disadvantages are recognized risks to mental health in the general population[26]. However, the effects of these determinants may be even more detrimental among childhood cancer survivors as these individuals, when assessed with comparative norms, experience an even greater risk of morbidity and adverse psychosocial outcomes[22–25,27–30]. Conversely, survivors who received some educational qualifications or worked in a managerial/professional position were found to exhibit less mental health dysfunction compared to their respective referents, which also generally corresponds with previous reports[10].

Limitations

Response bias due to selective responses should be minimal due to our reasonably good response rate and the fact that there was not a substantial difference in cancer and socio-demographic characteristics between responders and non-responders of our questionnaire[6]. There is potentially selection bias due to survival, particularly among the group of older survivors, as they may be healthier than their counterparts who did not survive until questionnaire send-out. Another limitation in our study is our comparison data, which may differ from our study population in terms of socio-economic status. However, as the results from our internal and external analyses broadly correspond with one another, confounding by this factor should be limited. Finally, although the findings from this paper may not be generalizable for children diagnosed with cancer after 1991, they are still highly relevant to children treated more recently for whom treatment intensity and long-term morbidity may be

greater. We acknowledge reassessment is necessary and recommend further analyses to be conducted on the recently extended BCCSS cohort, which includes five-year survivors diagnosed from 1992-2006, and other long-term follow-up studies.

Clinical Recommendations

Although the need for long-term psychological assessment and care is recognized[5,31–33], there remain uncertainties as to how these individuals should be assessed. A previous study reported that approximately only 35% of childhood cancer survivors in the UK were on hospital follow-up[34]. Consequently, as general practitioners provide health care for the majority of these survivors[35], routine psychological assessment, preferably using a standardized and validated measure, should be integrated into both long-term hospital follow-up clinics and general practitioner visits, especially for the vulnerable subgroup of survivors identified in this study. To date, psychological provisions are lacking in late effects services and are rare in the primary care setting. In order to improve mental health, it is essential that recommendations for risk-based care are readily available for general practitioners and ongoing communication is coordinated across all sites and services involved. Furthermore, surveillance for mental health dysfunction and recommended interventions should be included in the development of clinical guidelines, treatment summaries, and patient care plans. As the results from this study suggest mental health dysfunction is a concern across the lifespan for survivors, it is imperative that equitable psychological support is continuously available within general practices or specialist late effects services, irrespective of the amount of time that has passed since initial diagnosis, and that funding is allocated to allow for interventions. Finally, the findings presented in this study also stress the importance of educational attainment and employment on long-term mental health. Educational support and career

advisors should be provided during and after treatment to ensure that childhood cancer survivors achieve their full educational and employment potential and have the same likelihood of academic and professional success as their peers. By continually improving the standard of care for mental health in childhood cancer survivors, we work towards meeting the goal of psychosocial oncology research, which is to facilitate patients' adjustment to the short- and long-term consequences of their treatment, recovery, and survivorship so that quality-of-life is not reduced[36].

Conclusions

Based on the findings of this large population-based study, childhood cancer survivors report significantly higher levels of mental health dysfunction than those in the general population, where excesses were observed particularly among CNS and bone sarcoma survivors. Limitations were also observed to increase with age, and thus it is important to emphasize the need for mental health evaluation and services across the entire lifespan. There is evidence that low educational attainment and being unemployed or having never worked adversely impacts long-term mental health. These findings provide an evidence base for risk stratification and planning interventions.

	ROLE EMOTIONAL SCALE			SOCIAL FUNCTIONING SCALE		MENTAL HEALTH SCALE				
	Cut down on the amount of time you spent on work or other activities? (Question 5a)	**Accomplished less than you would like? (Question 5b)**	**Didn't do work or other activities as carefully as usual? (Question 5c)**	**Has your physical health or emotional problems interfered with your normal social activities? (Question 6)**	**Has your health limited your social activities? (Question 9j)**	**Have you been a very nervous person? (Question 9b)**	**Have you felt so down in the dumps that nothing could cheer you up? (Question 9c)**	**Have you felt calm and peaceful? (Question 9d)**	**Have you felt downhearted and low? (Question 9f)**	**Have you been a happy person? (Question 9h)**
Characteristic	No. Reporting Dysfunction/No. Responders (%)	No. Reporting Dysfunction/No. Responders (%)	No. Reporting Dysfunction/No. Responders (%)	No. Reporting Dysfunction/No. Responders (%)	No. Reporting Dysfunction/No. Responders (%)	No. Reporting Dysfunction/No. Responders (%)	No. Reporting Dysfunction/No. Responders (%)	No. Reporting Dysfunction/No. Responders (%)	No. Reporting Dysfunction/No. Responders (%)	No. Reporting Dysfunction/No. Responders (%)
Sex										
Male	610/5222 (11.7)	903/5221 (17.3)	670/5212 (12.9)	796/5300 (15.0)	847/5249 (16.1)	1328/5271 (25.2)	1018/5279 (19.3)	2000/5278 (37.9)	1530/5258 (29.1)	1139/5274 (21.6)
Female	846/4999 (16.9)	1155/4996 (23.1)	934/4974 (18.8)	1022/5081 (20.1)	1075/5026 (21.4)	1626/5065 (32.1)	1425/5064 (28.1)	2527/5062 (49.9)	1975/5050 (39.1)	1283/5065 (25.3)
First Primary Neoplasm Type										
Leukemia	321/2811 (11.4)	478/2812(17.0)	368/2801 (13.0)	410/2852 (14.4)	374/2821 (13.3)	848/2833 (29.9)	686/2842 (24.1)	1190/2836 (42.0)	977/2827 (34.6)	559/2836 (19.7)
Hodgkin Lymphoma	93/732 (12.7)	132/730 (18.1)	113/731 (15.5)	104/737 (14.1)	101/734 (13.8)	197/736 (26.8)	144/738 (19.5)	316/739 (42.8)	231/738 (31.3)	182/737 (24.7)
NHL	75/527 (14.2)	110/530 (20.8)	90/525 (17.1)	85/531 (16.0)	84/527 (15.9)	133/531 (25.1)	110/530 (20.8)	236/530 (44.5)	160/528 (30.3)	133/530 (25.1)
CNS	437/2153 (20.3)	585/2153 (27.2)	455/2145 (21.2)	575/2230 (25.8)	717/2190 (32.7)	771/2213 (34.8)	643/2212 (29.1)	1091/2216 (49.2)	887/2201 (40.5)	666/2219 (30.0)
Neuroblastoma	55/424 (13.0)	79/425 (18.6)	59/423 (14.0)	72/426 (16.9)	66/423 (15.6)	100/426 (23.5)	107/426 (25.1)	177/424 (41.8)	145/425 (34.1)	98/406(23.2)
Non-Heritable Retinoblastoma	47/407 (11.6)	69/405 (17.0)	51/405 (12.6)	53/407 (13.0)	53/404 (13.1)	109/406 (26.9)	86/406 (21.2)	174/406 (42.9)	132/406 (32.5)	94/406 (23.2)
Heritable Retinoblastoma	43/288 (14.9)	68/290 (23.5)	42/288 (14.6)	48/293 (16.4)	49/291 (16.8)	66/292 (22.6)	62/292 (21.2)	111/293 (37.9)	88/292 (30.1)	65/293 (22.2)
Wilms	119/939 (12.7)	153/935 (16.4)	132/934 (14.1)	139/945 (14.7)	129/935 (13.8)	244/941 (25.8)	197/941 (20.9)	396/941 (41.9)	276/940 (29.3)	186/938 (19.8)
Bone Sarcoma	75/404 (18.6)	97/403 (24.1)	74/401 (18.5)	100/410 (24.4)	114/407 (28.0)	107/409 (26.2)	96/409 (23.5)	199/410 (48.5)	139/408 (34.1)	113/410 (27.6)
Soft Tissue Sarcoma	100/697 (14.4)	138/696 (19.8)	120/696 (17.2)	117/702 (16.7)	122/701 (17.4)	179/703 (25.5)	145/703 (20.6)	299/701 (42.7)	229/699 (32.8)	156/701 (22.3)
Other	91/839(10.9)	149/838 (17.8)	100/837 (12.0)	115/848 (13.6)	113/842 (13.4)	200/846 (24.6)	167/844 (19.8)	338/844 (41.1)	241/844 (28.9)	170/844 (20.1)
Age at Diagnosis										
Mean (range)	7.1(0-14.9)	7(0-14.9)	6.9(0-14.9)	7.0(0-14.9)	7.2(0-14.9)	6.5(0-14.9)	6.5(0-14.9)	6.8(0-14.9)	6.7(0-14.9)	7(0-14.9)
0-4 years	595/4711 (12.6)	837/4707 (17.8)	687/4697 (14.6)	762/4781 (15.9)	768/4736 (16.2)	1361/4764 (28.6)	1136/4767 (23.8)	1983/4761 (41.7)	1555/4752 (32.7)	1024/4766 (21.5)
5-9 years	403/2710 (14.9)	578/2708 (21.3)	427/2703 (15.8)	497/2754 (18.1)	537/2720 (19.7)	805/2731 (29.5)	644/2734 (23.6)	1216/2739 (44.4)	941/2723 (34.6)	646/2730 (23.7)
10-14 years	458/2800 (16.4)	643/2802 (23.0)	490/2786 (17.6)	559/2846 (19.6)	617/2819 (21.9)	788/2841 (27.7)	663/2842 (23.3)	1328/2840 (46.8)	1009/2833 (35.6)	752/2843 (26.5)
Radiotherapy										
No	313/2206 (14.2)	455/2210 (20.6)	336/2203 (15.3)	381/2233 (17.1)	430/2214 (19.4)	617/2232 (27.6)	534/2229 (24.0)	989/2227 (44.4)	770/2225 (34.6)	548/2226 (24.6)
Yes	782/5144 (15.2)	1079/5140 (21.0)	837/5119 (16.4)	999/5249 (19.0)	1060/5188 (20.4)	1500/5213 (28.8)	1263/5224 (24.2)	2329/5221 (44.6)	1828/5203 (35.1)	1255/5219 (24.1)
Chemotherapy										
No	535/3249 (16.5)	745/3248 (22.9)	556/3240 (17.2)	674/3322 (20.3)	802/3279 (24.5)	941/3309 (28.4)	809/3305 (24.5)	1505/3303 (45.6)	1186/3295 (36.0)	873/3305 (26.4)
Yes	510/7122 (13.2)	722/3872 (18.7)	574/3854 (14.9)	638/3918 (16.3)	612/3886 (15.8)	1104/3901 (28.3)	921/3910 (23.6)	1684/3907 (43.1)	1315/3895 (33.8)	843/3901 (21.6)
Surgery										
No	438/3353 (13.1)	625/3353 (18.6)	486/3340 (14.6)	864/4286 (20.2)	968/4235 (22.9)	980/3386 (28.9)	820/3393 (24.2)	1485/3390 (43.8)	1186/3383 (35.1)	1090/4268 (25.5)
Yes	679/4202 (16.2)	944/4200 (22.5)	713/4186 (17.0)	548/3402 (16.1)	546/3369 (16.2)	1198/4266 (28.1)	1018/4266 (23.9)	1928/4264 (45.2)	1478/4251 (34.8)	762/3384 (22.5)

Table 4.1: Frequency of reporting mental health dysfunction in the ten questions under investigation among survivors of childhood cancer in the British Childhood Cancer Survivor Study

	ROLE EMOTIONAL SCALE			SOCIAL FUNCTIONING SCALE		MENTAL HEALTH SCALE				
	Cut down on the amount of time you spent on work or other activities? (Question 5a)	**Accomplished less than you would like? (Question 5b)**	**Didn't do work or other activities as carefully as usual? (Question 5c)**	**Has your physical health or emotional problems interfered with your normal social activities? (Question 6)**	**Has your health limited your social activities? (Question 9j)**	**Have you felt so down in the dumps that nothing could cheer you up? (Question 9c)**	**Have you felt calm and peaceful? (Question 9d)**	**Have you felt downhearted and low? (Question 9f)**	**Have you been a happy person? (Question 9h)**	**Accomplished less than you would like? (Question 5b)**
Characteristic	No. Reporting Dysfunction/No. Responders (%)	No. Reporting Dysfunction/No. Responders (%)	No. Reporting Dysfunction/No. Responders (%)	No. Reporting Dysfunction/No. Responders (%)	No. Reporting Dysfunction/No. Responders (%)	No. Reporting Dysfunction/No. Responders (%)	No. Reporting Dysfunction/No. Responders (%)	No. Reporting Dysfunction/No. Responders (%)	No. Reporting Dysfunction/No. Responders (%)	No. Reporting Dysfunction/No. Responders (%)
Age at Questionnaire Completion										
Mean (range)	31.7(16.0-66.1)	31.5(16.0-66.1)	31.0(16.0-66.1)	31.5(16.0-70.0)	32.4(16.0-7.0)	29.7(16.0-70.0)	29.9(16.0-66.1)	30.6(16.0-70.0)	30.6(16.0-66.1)	31.5(16.1-70.0)
16-24 years	435/3704 (11.7)	643/3695 (17.4)	521/3693 (14.1)	549/3741 (14.7)	518/3705 (14.0)	1113/3727 (29.9)	864/3724 (23.2)	1505/3728 (40.4)	1182/3716 (31.8)	744/3726 (20.0)
25-34 years	523/3531 (14.8)	714/3529 (20.2)	562/3519 (16.0)	657/3587 (18.3)	705/3552 (19.9)	1038/3567 (29.1)	894/3579 (25.0)	1626/3572 (45.5)	1265/3564 (35.5)	862/3572 (24.1)
35-44 years	325/1976 (16.5)	456/1981 (23.0)	349/1973 (17.7)	400/2024 (19.8)	443/2008 (22.1)	533/2021 (26.4)	496/2023 (24.5)	956/2021 (47.3)	712/2013 (35.4)	538/2021 (26.6)
45+ years	173/1010 (17.1)	245/1012 (24.2)	172/1001 (17.2)	212/1029 (20.6)	256/1010 (25.4)	270/1021 (26.4)	189/1017 (18.6)	440/1019 (43.2)	346/1015 (34.1)	278/1020 (27.3)
Marital Status										
Single	785/5629 (14.0)	1125/5629 (20.0)	908/5619 (16.2)	1026/5741 (17.9)	1070/5674 (18.9)	1756/5705 (30.8)	1423/5717 (24.9)	2437/5712 (42.7)	1967/5695 (34.5)	1318/5715 (23.1)
Cohabiting	166/1034 (16.1)	229/1029 (22.3)	170/1029 (16.5)	192/1043 (18.4)	187/1036 (18.1)	264/1043 (25.3)	254/1043 (24.4)	492/1041 (47.3)	375/1042 (36.0)	269/1038 (25.9)
Married	338/2703 (12.5)	473/2702 (17.5)	345/2689 (12.8)	408/2723 (15.0)	451/2704 (16.7)	645/2720 (23.7)	500/2717 (18.4)	1172/2717 (43.1)	792/2711 (29.2)	561/2716 (20.7)
Separated	35/149 (23.5)	50/150 (33.3)	39/148 (26.4)	36/150 (24.0)	36/148 (24.3)	54/150 (36.0)	51/149 (34.2)	81/150 (54.0)	79/148 (53.4)	49/149 (32.9)
Divorced	86/440 (19.6)	118/442 (26.7)	93/438 (21.2)	104/447 (23.3)	112/442 (25.3)	145/444 (32.6)	132/441 (29.9)	217/444 (48.9)	182/444 (41.0)	144/445 (32.4)
Widowed	6/32 (18.8)	8/32 (25.0)	9/32 (28.1)	8/32 (25.0)	13/33 (39.4)	10/33 (30.3)	13/33(39.4)	17/33 (51.5)	13/32 (40.6)	11/33 (33.3)
Educational Attainment										
No qualifications	328/1433 (22.9)	416/1434 (29.0)	334/1418 (23.6)	453/1518 (29.8)	530/1475 (35.9)	544/1491 (36.5)	505/1489 (33.9)	761/1493 (51.0)	635/1482 (42.9)	456/1491 (30.6)
Other qualifications	219/1424 (15.4)	297/1421 (20.9)	231/1414 (16.3)	289/1447 (20.0)	312/1432 (21.8)	4991435 (34.8)	417/1441 (28.9)	649/1439 (45.1)	541/1433 (37.8)	375/1440 (26.0)
O-level	357/2836 (12.6)	516/2839 (18.2)	419/2837 (14.8)	433/2858 (15.2)	467/2835 (16.5)	780/2860 (27.3)	662/2855 (23.2)	1204/2858 (42.1)	972/2851 (34.1)	635/2853 (22.3)
A-level	236/1919 (12.3)	358/1921 (18.6)	258/1917 (13.5)	274/1928 (14.2)	244/1916 (12.7)	493/1923 (25.6)	370/1928 (19.2)	786/1926 (40.8)	581/1922 (30.2)	400/1925 (20.8)
Teaching	111/919 (12.1)	158/917 (17.2)	128/917 (14.0)	124/919 (13.5)	136/913 (14.9)	236/914 (25.8)	177/918 (19.3)	392/918 (42.7)	282/914 (30.9)	195/916 (21.3)
Degree	151/1416 (10.7)	248/1416 (17.5)	173/1416 (12.2)	176/1423 (12.4)	156/1415 (11.0)	299/1426 (21.0)	225/1423 (15.8)	610/1425 (42.8)	390/1420 (27.5)	290/1424(20.4)
Socioeconomic Classification										
Student	206/1728 (11.9)	315/1725 (18.3)	241/1720 (14.0)	249/1738 (14.3)	232/1725 (13.5)	524/1733 (30.2)	351/1733 (20.3)	679/1734 (39.2)	512/1724 (29.7)	313/1733 (18.1)
Never worked/ Unemployed	130/576 (22.6)	179/579 (30.9)	125/576 (21.7)	174/603 (28.9)	191/600 (31.8)	231/60 (38.5)	244/604 (40.4)	295/603 (48.9)	252/601 (41.9)	203/601 (33.8)
Routine/Manual	435/3086 (14.1)	598/3080 (19.4)	501/3071 (16.3)	540/3121 (17.3)	589/3083 (19.1)	944/3105 (30.4)	799/3103 (25.8)	1353/3102 (43.6)	1134/3102 (36.6)	754/3106 (24.3)
Intermediate	253/1840 (13.8)	365/1842 (19.8)	264/1838(14.4)	307/1847 (16.6)	316/1834 (17.2)	485/1844(26.3)	388/1843 (21.1)	807/1846 (43.7)	621/1836 (33.8)	423/1843 (23)
Managerial/ Professional	236/2344 (10.1)	376/2345 (16.0)	276/2343 (11.8)	279/2353 (11.9)	275/2334 (11.8)	500/2354 (21.2)	382/2352 (16.2)	985/2352 (41.9)	645/2346 (27.5)	478/2349 (20.4)

Table 4.1 (*continued):* Frequency of reporting mental health dysfunction in the ten questions under investigation among survivors of childhood cancer in the British Childhood Cancer Survivor Study

Abbreviations: NHL: non-Hodgkin lymphoma, CNS: central nervous system

Characteristic	Cut down on the amount of time you spent on work or other activities? (Question 5a)			Accomplished less than you would like? (Question 5b)			Didn't do work or other activities as carefully as usual? (Question 5c)		
	OR (95%CI)	*P*	*P*heterogeneity† (*P*trend‡)	OR (95%CI)	*P*	*P*heterogeneity† (*P*trend‡)	OR (95%CI)	*P*	*P*heterogeneity† (*P*trend‡)
Sex									
Male	1.0			1.0			1.0		
Female	1.6 (1.4,1.8)	<0.001	<0.0001	1.5 (1.3,1.7)	<0.001	<0.0001	1.8 (1.6,2.0)	<0.001	<0.0001
First Primary Neoplasm Type									
Leukemia	1.0			1.0			1.0		
Hodgkin Lymphoma	1.2 (0.9,1.5)	0.317		1.0 (0.8,1.3)	0.723		1.4 (1.0,1.8)	0.024	
NHL	1.4 (1.1,1.9)	0.019		1.4 (1.1,1.7)	0.019		1.6 (1.2,2.1)	0.001	
CNS	1.6 (1.4,2.0)	<0.001		1.5 (1.2,1.7)	<0.001		1.5 (1.2,1.8)	<0.001	
Neuroblastoma	1.4 (1.0,1.9)	0.055		1.3 (1.0,1.7)	0.077		1.1 (0.8,1.6)	0.437	
Non-Heritable Retinoblastoma	1.1 (0.8,1.6)	0.496		1.1 (0.8,1.5)	0.687		1.0 (0.7,1.4)	0.967	
Heritable Retinoblastoma	1.7 (1.1,2.4)	0.011		1.7 (1.2,2.3)	0.002		1.3 (0.9,1.9)	0.205	
Wilms	1.2 (1.0,1.6)	0.105		1.0 (0.8,1.3)	0.838		1.1 (0.9,1.5)	0.256	
Bone Sarcoma	1.7 (1.2,2.4)	0.001		1.4 (1.1,1.9)	0.014		1.5 (1.1,2.1)	0.008	
Soft Tissue Sarcoma	1.5 (1.1,1.9)	0.006		1.2 (1.0,1.5)	0.082		1.5 (1.1,1.9)	0.003	
Other	0.9 (0.7,1.2)	0.673	<0.0001	1.0 (0.8,1.3)	0.693	<0.0001	1.0 (0.8,1.3)	0.927	0.0005
Age at Diagnosis									
0-4 years	1.0			1.0			1.0		
5-9 years	1.2 (1.0,1.4)	0.029		1.3 (1.1,1.5)	0.001		1.1 (0.9,1.2)	0.530	
10-14 years	1.2 (1.0,1.5)	0.026	0.0462 (0.0282)	1.3 (1.1,1.5)	0.003	0.0019 (0.0029)	1.1 (1.0,1.4)	0.147	0.3433 (0.1380)
Age at Questionnaire Completion									
16-24 years	1.0			1.0			1.0		
25-34 years	1.4 (1.1,1.7)	0.001		1.3 (1.1,1.5)	0.001		1.3 (1.1,1.5)	0.009	
35-44 years	1.6 (1.2,2.0)	<0.001		1.6 (1.3,2.0)	<0.001		1.4 (1.2,1.8)	0.001	
45+ years	1.4 (1.1,1.9)	0.012	0.0016 (0.0004)	1.6 (1.2,2.0)	<0.001	<0.0001 (<0.0001)	1.2 (0.9,1.6)	0.124	0.0087 (0.0054)
Marital Status									
Single	1.0			1.0			1.0		
Cohabiting	1.1 (0.9,1.4)	0.226		1.1 (0.9,1.4)	0.166		1.0 (0.8,1.2)	0.971	
Married	0.7 (0.6,0.9)	0.002		0.7 (0.6,0.8)	<0.001		0.7 (0.5,0.8)	<0.001	
Separated	1.5 (1.0,2.4)	0.047		1.6 (1.1,2.4)	0.013		1.6 (1.0,2.3)	0.031	
Divorced	1.2 (0.9,1.6)	0.333		1.1 (0.8,1.4)	0.495		1.1 (0.8,1.4)	0.613	
Widowed	0.7 (0.2,2.2)	0.603	0.0001	0.8 (0.3,2.0)	0.583	<0.0001	1.1 (0.4,2.9)	0.817	<0.0001
Educational Attainment									
No qualifications	1.0			1.0			1.0		
Other qualifications	0.7 (0.6,0.9)	0.010		0.8 (0.6,0.9)	0.010		0.8 (0.6,1.0)	0.040	
O-level	0.7 (0.5,0.8)	<0.001		0.7 (0.6,0.8)	<0.001		0.8 (0.6,0.9)	0.005	
A-level	0.7 (0.6,0.9)	0.001		0.7 (0.6,0.9)	0.002		0.7 (0.6,0.9)	0.003	
Teaching qualification	0.6 (0.5,0.8)	0.002		0.7 (0.5,0.8)	0.001		0.8 (0.6,1.0)	0.037	
Degree	0.6 (0.5,0.8)	<0.001	0.0004	0.7 (0.6,0.9)	0.003	0.0044	0.7 (0.5,0.9)	0.002	0.0030
Socioeconomic Classification									
Student	1.0			1.0			1.0		
Never worked/Unemployed	1.5 (1.2,2.0)	0.003		1.4 (1.1,1.8)	0.003		1.3 (1.0,1.8)	0.030	
Routine/Manual	0.9 (0.7,1.1)	0.424		0.8 (0.7,1.0)	0.030		1.0 (0.8,1.2)	0.893	
Intermediate	0.9 (0.7,1.1)	0.290		0.8 (0.7,1.0)	0.060		0.8 (0.7,1.1)	0.155	
Managerial/Professional	0.7 (0.5,0.9)	0.005	<0.0001	0.7 (0.5,0.8)	<0.001	<0.0001	0.8 (0.6,1.0)	0.025	0.0004

Table 4.2: Multivariable logistic regression models* reporting odds ratios and 95% confidence intervals for reporting mental health dysfunction within the three questions comprising the role emotional scale of the SF-36 survey, by specific potential demographic, cancer, social, and economic factors

Abbreviations: NHL: non-Hodgkin lymphoma, CNS: central nervous system, OR: odds ratio, CI: confidence intervals

*Adjusted for age at diagnosis, diagnosis, sex, age at questionnaire completion, marital status, educational attainment, and socioeconomic classification

†The *P*heterogeneity (two-sided) is from the likelihood ratio test for heterogeneity in the probability of reporting mental health dysfunction within this specific question, across different levels of the specified explanatory factor with adjustment for all other factors in the multivariate model. The threshold for statistical significant was 0.05.

‡The *P*trend (two-sided) is from the test for trend, where the threshold for statistical significant was 0.05.

Characteristic	Has your physical health or emotional problems interfered with your normal social activities? (Question 6)			Has your health limited your social activities? (Question 9j)		
	OR (95%CI)	*P*	*P*heterogeneity† (*P*trend‡)	OR (95%CI)	*P*	*P*heterogeneity† (*P*trend‡)
Sex						
Male	1.0			1.0		
Female	1.5 (1.3,1.7)	<0.001	<0.0001	1.5 (1.4,1.7)	<0.001	<0.0001
First Primary Neoplasm Type						
Leukemia	1.0			1.0		
Hodgkin Lymphoma	0.9 (0.7,1.2)	0.703		1.2 (0.9,1.5)	0.284	
NHL	1.3 (1.0,1.7)	0.079		1.5 (1.1,2.0)	0.004	
CNS	1.6 (1.4,1.9)	<0.001		2.5 (2.1,2.9)	<0.001	
Neuroblastoma	1.5 (1.1,2.0)	0.011		1.5 (1.1,2.0)	0.020	
Non-Heritable Retinoblastoma	1.0 (0.7,1.4)	0.812		1.0 (0.7,1.5)	0.864	
Heritable Retinoblastoma	1.3 (0.9,1.9)	0.197		1.5 (1.0,2.2)	0.037	
Wilms	1.1 (0.8,1.3)	0.896		1.1 (0.9,1.5)	0.275	
Bone Sarcoma	2.0 (1.5,2.7)	<0.001		3.0 (2.3,4.0)	<0.001	
Soft Tissue Sarcoma	1.3 (1.0,1.7)	0.036		1.6 (1.2,2.0)	<0.001	
Other	1.0 (0.7,1.2)	0.692	<0.0001	1.2 (0.9,1.5)	0.224	<0.0001
Age at Diagnosis						
0-4 years	1.0			1.0		
5-9 years	1.1 (0.9,1.3)	0.377		1.1 (0.9,1.2)	0.462	
10-14 years	1.1 (1.0,1.4)	0.137	0.3297 (0.1368)	1.1 (0.9,1.3)	0.258	0.5227 (0.2821)
Age at Questionnaire Completion						
16-24 years	1.0			1.0		
25-34 years	1.5 (1.3,1.8)	<0.001		1.8 (1.5,2.2)	<0.001	
35-44 years	1.6 (1.3,1.8)	<0.001		2.0 (1.6,2.5)	<0.001	
45+ years	1.5 (1.2,2.0)	0.002	<0.0001 (<0.0001)	2.1 (1.6,2.7)	<0.001	<0.0001 (<0.0001)
Marital Status						
Single	1.0			1.0		
Cohabiting	1.1 (0.9,1.3)	0.419		1.0 (0.8,1.2)	0.940	
Married	0.7 (0.6,0.9)	<0.001		0.7 (0.6,0.8)	<0.001	
Separated	1.3 (0.9,2.0)	0.176		1.2 (0.8,1.8)	0.447	
Divorced	1.1 (0.9,1.5)	0.339		1.0 (0.8,1.3)	0.969	
Widowed	1.2 (0.5,2.9)	0.709	0.0001	1.6 (0.7,3.8)	0.255	0.0001
Educational Attainment						
No qualifications	1.0			1.0		
Other qualifications	0.7 (0.6,0.9)	<0.001		0.7 (0.6,0.8)	<0.001	
O-level	0.6 (0.5,0.7)	<0.001		0.5 (0.4,0.6)	<0.001	
A-level	0.6 (0.5,0.7)	<0.001		0.4 (0.4,0.5)	<0.001	
Teaching qualification	0.5 (0.4,0.7)	<0.001		0.5 (0.4,0.6)	<0.001	
Degree	0.5 (0.4,0.6)	<0.001	<0.0001	0.4 (0.3,0.5)	<0.001	<0.0001
Socioeconomic Classification (SEC)						
Student	1.0			1.0		
Never worked/Unemployed	1.6 (1.3,2.1)	<0.001		1.7 (1.3,2.2)	<0.001	
Routine/Manual	0.9 (0.7,1.1)	0.384		0.9 (0.7,1.1)	0.402	
Intermediate	0.9 (0.7,1.1)	0.329		0.9 (0.7,1.1)	0.224	
Managerial/Professional	0.7 (0.5,0.9)	0.001	<0.0001	0.7 (0.5,0.9)	<0.001	<0.0001

Table 4.3: Multivariable logistic regression models* reporting odds ratios and 95% confidence intervals for reporting mental health dysfunction within the two questions comprising the social functioning scale of the SF-36 survey, by specific potential demographic, cancer, social, and economic factors

Abbreviations: NHL: non-Hodgkin lymphoma, CNS: central nervous system, OR: odds ratio, CI: confidence intervals

*Adjusted for age at diagnosis, diagnosis, sex, age at questionnaire completion, marital status, educational attainment, and socioeconomic classification

†The *P*heterogeneity (two-sided) is from the likelihood ratio test for heterogeneity in the probability of reporting mental health dysfunction within this specific question, across different levels of the specified explanatory factor with adjustment for all other factors in the multivariate model. The threshold for statistical significant was 0.05.

‡The *P*trend (two-sided) is from the test for trend, where the threshold for statistical significant was 0.05.

Characteristic	Have you been a very nervous person? (Question 9b)			Have you felt so down in the dumps that nothing could cheer you up? (Question 9c)			Have you felt calm and peaceful? (Question 9d)			Have you felt downhearted and low? (Question 9f)			Have you been a happy person? (Question 9h)		
	OR (95%CI)	*P*	*P*heterogeneity† (*P*trend‡)	OR (95%CI)	*P*	*P*heterogeneity† (*P*trend‡)	OR (95%CI)	*P*	*P*heterogeneity† (*P*trend‡)	OR (95%CI)	*P*	*P*heterogeneity† (*P*trend‡)	OR (95%CI)	*P*	*P*heterogeneity† (*P*trend‡)
Sex															
Male	1.0			1.0			1.0			1.0			1.0		
Female	1.4 (1.3,1.6)	<0.001	<0.0001	1.7 (1.5,1.9)	<0.001	<0.0001	1.6 (1.5,1.8)	<0.001	<0.0001	1.6 (1.4,1.7)	<0.001	<0.0001	1.2 (1.1,1.4)	<0.001	<0.0001
First Primary Neoplasm Type															
Leukemia	1.0			1.0			1.0			1.0			1.0		
Hodgkin Lymphoma	1.1 (0.9,1.3)	0.433		1.0 (0.8,1.2)	0.732		1.1 (0.9,1.3)	0.468		1.0 (0.8,1.2)	0.617		1.3 (1.0,1.6)	0.021	
NHL	1.0 (0.8,1.2)	0.863		1.1 (0.8,1.4)	0.620		1.2 (1.0,1.5)	0.086		0.9 (0.8,1.2)	0.615		1.4 (1.1,1.8)	0.003	
CNS	1.3 (1.1,1.5)	0.001		1.2 (1.0,1.4)	0.036		1.2 (1.0,1.3)	0.024		1.1 (1.0,1.3)	0.080		1.4 (1.2,1.6)	<0.001	
Neuroblastoma	0.8 (0.6,1.1)	0.116		1.2 (0.9,1.6)	0.124		1.1 (0.9,1.3)	0.535		1.1 (0.9,1.4)	0.432		1.3 (1.0,1.7)	0.041	
Non-Heritable Retinoblastoma	1.1 (0.8,1.3)	0.884		1.0 (0.8,1.4)	0.737		1.1 (0.9,1.4)	0.373		1.1 (0.8,1.3)	0.681		1.4 (1.0,1.8)	0.024	
Heritable Retinoblastoma	0.8 (0.6,1.1)	0.242		1.1 (0.8,1.5)	0.518		0.8 (0.6,1.1)	0.242		0.9 (0.7,1.2)	0.612		1.2 (0.9,1.6)	0.311	
Wilms	0.9 (0.8,1.1)	0.249		0.9 (0.8,1.2)	0.586		1.0 (0.9,1.2)	0.896		0.8 (0.7,1.0)	0.065		1.0 (0.8,1.2)	0.989	
Bone Sarcoma	1.0 (0.8,1.3)	0.881		1.2 (0.9,1.6)	0.229		1.2 (1.0,1.6)	0.071		1.0 (0.8,1.3)	0.737		1.5 (1.1,1.9)	0.005	
Soft Tissue Sarcoma	0.9 (0.7,1.1)	0.398		1.0 (0.8,1.2)	0.853		1.1 (0.9,1.3)	0.491		1.0 (0.8,1.2)	0.877		1.2 (1.0,1.5)	0.085	
Other	0.9 (0.7,1.1)	0.174	0.0022	0.9 (0.8,1.1)	0.481	0.2762	0.9 (0.8,1.1)	0.379	0.1254	0.8 (0.7,1.0)	0.015	0.0273	1.0 (0.8,1.2)	0.898	0.0004
Age at Diagnosis															
0-4 years	1.0			1.0			1.0			1.0			1.0		
5-9 years	1.1 (0.9,1.2)	0.412		1.0 (0.9,1.2)	0.527		1.0 (0.9,1.2)	0.423		1.1 (1.0,1.2)	0.200		1.0 (0.9,1.2)	0.618	
10-14 years	1.0 (0.9,1.2)	0.708	0.7132 (0.7301)	1.1 (0.9,1.3)	0.334	0.6190 (0.3569)	1.1 (1.0,1.3)	0.094	0.2444 (0.1029)	1.1 (1.0,1.3)	0.098	0.2266 (0.1072)	1.1 (1.0,1.3)	0.132	0.2990 (0.1519)
Age at Questionnaire Completion															
16-24 years	1.0			1.0			1.0			1.0			1.0		
25-34 years	1.1 (1.0,1.3)	0.131		1.2 (1.0,1.4)	0.21		1.2 (1.0,1.3)	0.010		1.3 (1.1,1.5)	<0.001		1.3 (1.1,1.5)	0.001	
35-44 years	1.0 (0.9,1.2)	0.852		1.2 (1.0,1.4)	0.103		1.3 (1.1,1.5)	0.002		1.3 (1.1,1.6)	0.001		1.5 (1.3,1.9)	<0.001	
45+ years	1.0 (0.8,1.2)	0.666	0.2051 (0.8380)	0.8 (0.6,1.0)	0.050	0.0001 (0.7357)	1.0 (0.8,1.3)	0.731	0.0021 (0.0415)	1.2 (1.0,1.5)	0.078	0.0013 (0.0015)	1.6 (1.2,2.0)	<0.001	<0.0001 (<0.0001)

Table 4.4*:* Multivariable logistic regression models* reporting odds ratios and 95% confidence intervals for reporting mental health dysfunction within the five questions comprising the mental health scale of the SF-36 survey, by specific potential demographic, cancer, social, and economic factors

Abbreviations: NHL: non-Hodgkin lymphoma, CNS: central nervous system, OR: odds ratio, CI: confidence intervals

*Adjusted for age at diagnosis, diagnosis, sex, age at questionnaire completion, marital status, educational attainment, and socioeconomic classification

†The *P*heterogeneity (two-sided) is from the likelihood ratio test for heterogeneity in the probability of reporting mental health dysfunction within this specific question, across different levels of the specified explanatory factor with adjustment for all other factors in the multivariate model. The threshold for statistical significant was 0.05.

‡The *P*trend (two-sided) is from the test for trend, where the threshold for statistical significant was 0.05.

Characteristic	Have you been a very nervous person? (Question 9b)			Have you felt so down in the dumps that nothing could cheer you up? (Question 9c)			Have you felt calm and peaceful? (Question 9d)			Have you felt downhearted and low? (Question 9f)			Have you been a happy person? (Question 9h)		
	OR (95%CI)	*P*	*P*heterogeneity† (*P*trend‡)	OR (95%CI)	*P*	*P*heterogeneity† (*P*trend‡)	OR (95%CI)	*P*	*P*heterogeneity† (*P*trend‡)	OR (95%CI)	*P*	*P*heterogeneity† (*P*trend‡)	OR (95%CI)	*P*	*P*heterogeneity† (*P*trend‡)
Marital Status															
Single	1.0			1.0			1.0			1.0			1.0		
Cohabiting	0.8 (0.7,1.0)	0.018		1.0 (0.8,1.2)	0.700		1.1 (1.0,1.3)	0.159		1.0 (0.8,1.2)	0.879		1.1 (0.9,1.3)	0.519	
Married	0.7 (0.6,0.8)	<0.001		0.6 (0.5,0.7)	<0.001		0.9 (0.8,1.0)	0.091		0.7 (0.6,0.8)	<0.001		0.7 (0.6,0.8)	<0.001	
Separated	1.2 (0.8,1.7)	0.305		1.3 (0.9,1.9)	0.149		1.3 (0.9,1.9)	0.098		1.7 (1.2,2.4)	0.003		1..3 (0.9,1.9)	0.175	
Divorced	1.0 (0.8,1.3)	0.916		1.1 (0.8,1.4)	0.588		1.0 (0.8,1.3)	0.822		1.0 (0.8,1.2)	0.872		1.1 (0.9,1.4)	0.469	
Widowed	0.9 (0.4,2.1)	0.810	<0.0001	2.1 (0.9,4.6)	0.074	<0.0001	1.3 (0.6,2.9)	0.455	0.0306	1.1 (0.5,2.3)	0.893	<0.0001	1.1 (0.5,2.5)	0.852	<0.0001
Educational Attainment															
No qualifications	1.0			1.0			1.0			1.0			1.0		
Other qualifications	1.0 (0.9,1.2)	0.719		0.9 (0.7,1.0)	0.123		0.9 (0.7,1.0)	0.054		0.9 (0.8,1.1)	0.230		0.9 (0.7,1.1)	0.218	
O-level	0.8 (0.7,0.9)	0.001		0.7 (0.6,0.8)	<0.001		0.8 (0.7,0.9)	0.004		0.8 (0.7,1.0)	0.013		0.8 (0.7,0.9)	0.010	
A-level	0.7 (0.6,0.9)	<0.001		0.6 (0.5,0.8)	<0.001		0.8 (0.7,0.9)	0.004		0.7 (0.6,0.9)	<0.001		0.8 (0.6,0.9)	0.005	
Teaching qualification	0.8 (0.6,1.0)	0.029		0.6 (0.5,0.8)	<0.001		0.8 (0.7,1.0)	0.031		0.8 (0.6,0.9)	0.006		0.7 (0.6,0.9)	0.009	
Degree	0.6 (0.5,0.8)	<0.001	<0.0001	0.5 (0.4,0.6)	<0.001	<0.0001	0.8 (0.7,1.0)	0.047	0.0646	0.7 (0.6,0.8)	<0.001	<0.0001	0.7 (0.6,0.9)	0.002	0.0007
Socioeconomic Classification															
Student	1.0			1.0			1.0			1.0			1.0		
Never worked/ Unemployed	1.3 (1.1,1.6)	0.008		2.6 (2.1,3.2)	<0.001		1.3 (1.1,1.6)	0.006		1.5 (1.2,1.8)	<0.001		1.8 (1.5,2.3)	<0.001	
Routine/ Manual	1.0 (0.9,1.2)	0.892		1.4 (1.2,1.7)	<0.001		1.1 (0.9,1.2)	0.417		1.3 (1.1,1.5)	0.004		1.2 (1.0,1.4)	0.091	
Intermediate	0.9 (0.7,1.0)	0.153		1.1 (0.9,1.4)	0.245		1.0 (0.9,1.2)	0.986		1.1 (0.9,1.3)	0.195		1.1 (0.9,1.3)	0.430	
Managerial/ Professional	0.8 (0.6,0.9)	0.009	<0.0001	1.0 (0.8,1.3)	0.766	<0.0001	1.0 (0.8,1.2)	0.816	0.0339	0.9 (0.8,1.1)	0.527	<0.0001	1.0 (0.8,1.2)	0.973	<0.0001

Table 4.4 (*continued*): Multivariable logistic regression models* reporting odds ratios and 95% confidence intervals for reporting mental health dysfunction within the five questions comprising the mental health scale of the SF-36 survey, by specific potential demographic, cancer, social, and economic factors.

Abbreviations: NHL: non-Hodgkin lymphoma, CNS: central nervous system, OR: odds ratio, CI: confidence intervals

*Adjusted for age at diagnosis, diagnosis, sex, age at questionnaire completion, marital status, educational attainment, and socioeconomic classification

†The *P*heterogeneity (two-sided) is from the likelihood ratio test for heterogeneity in the probability of reporting mental health dysfunction within this specific question, across different levels of the specified explanatory factor with adjustment for all other factors in the multivariate model. The threshold for statistical significant was 0.05.

‡The *P*trend (two-sided) is from the test for trend, where the threshold for statistical significant was 0.05.

Question	General Population Sample	All Survivors	Leukemia	HL	NHL	CNS	Neuroblastoma	NH-Retinoblastoma	H-Retinoblastoma	Wilms	Bone Sarcoma	STS	Other
Cut down on the amount of time you spent on work or other activities? (Question 5a)	12.7 (12.0,13.4)	16.2 (15.0,17.4)	10.6 (7.8,13.5)	13 (9.4,17.7)	14.9 (10.5,19.2)	21.6 (19.2,24.0)	14.9 (10.2,19.7)	11.2 (6.7,15.7)	18.1 (11.4,24.8)	14.1 (9.4,18.8)	20.8 (15.7,25.8)	18.2 (13.8,22.7)	11.6 (8.7,14.6)
Accomplished less than you would like? (Question 5b)	21.6 (20.7,22.4)	22.7 (21.4,24.1)	19.0 (16.1,22.0)	18.9 (14.3,23.4)	24.2 (18.8,29.7)	28.4 (25.8,31.0)	16.1 (12.2,20.0)	19.4 (14.6,24.1)	27.9 (20.4,35.4)	21.5 (15.3,27.8)	26.0 (20.7,31.3)	22.2 (17.6,26.8)	19.1 (15.7,22.5)
Didn't do work or other activities as carefully as usual? (Question 5c)	17.6 (16.8,18.3)	17.3 (16.0,18.5)	11.3 (8.4,14.1)	18.7 (13.8,23.6)	17.5 (12.9,22.1)	22.0 (19.6,24.5)	12.9 (9.1,16.8)	13.8 (8.8,18.8)	16.7 (10.1,23.3)	17.9 (12.0,23.8)	19.2 (14.4,24.0)	19.2 (14.6,23.7)	12.5 (9.5,15.5)
Has your physical health or emotional problems interfered with your normal social activities? (Question 6)	14.7 (14.0,15.5)	19.9 (18.6,21.2)	16.2 (13.4,19.0)	14.7 (10.4,18.9)	21.4 (16.3,26.5)	26.0 (23.5,28.4)	17.1 (10.5,23.7)	14.7 (9.6,19.8)	18.7 (12.9,24.4)	15.0 (10.5,19.6)	25.4 (20.2,30.6)	20.9 (16.2,25.6)	15.2 (11.9,18.6)
Has your health limited your social activities? (Question 9j)	13.2 (12.5,13.9)	23.1 (21.8,24.5)	16.0 (13.2,18.8)	14.8 (10.5,19.1)	23.3 (18.2,28.4)	35.5 (32.8,38.2)	14.2 (10.3,18.2)	16.9 (11.2,22.6)	19.9 (12.9,27.0)	21.2 (14.8,27.6)	29.1 (23.6,34.7)	20.9 (16.3,25.6)	16.7 (13.1,20.3)
Have you been a very nervous person? (Question 9b)	20.6 (19.8,21.5)	28.3 (26.9,29.7)	25.1 (21.6,28.6)	27.5 (22.2,32.8)	25.8 (20.7,30.9)	36.2 (33.5,38.9)	19.4 (14.0,24.7)	25.7 (19.7,31.8)	20.4 (14.7,26.0)	24.0 (18.2,29.8)	23.5 (19.1,28.0)	26.6 (21.7,31.5)	23.3 (19.8,26.9)
Have you felt so down in the dumps that nothing could cheer you up? (Question 9c)	18.3 (17.5,19.0)	22.8 (21.6,24.0)	22.3 (19.3,25.2)	18.9 (14.5,23.3)	22.6 (17.6,27.6)	28.2 (25.7,30.7)	22.3 (17.6,27.0)	19.3 (14.3,24.3)	22.5 (15.5,29.5)	20.5 (15.5,25.5)	25.2 (19.9,30.5)	20.9 (16.5,25.4)	17.4 (14.7,20.1)
Have you felt calm and peaceful? (Question 9d)	43.3 (42.3,44.4)	45.1 (43.6,46.6)	39.5 (35.6,43.5)	45.3 (40.1,50.5)	45.9 (40.2,51.7)	49.2 (46.4,52.0)	42.2 (33.8,50.6)	44.3 (38.1,50.5)	34.4 (28.2,40.5)	45.1 (38.6,51.5)	50.2 (44.3,56.1)	43.0 (37.8,48.1)	40.3 (36.2,44.4)
Have you felt downhearted and low? (Question 9f)	28.3 (27.4,29.2)	35.2 (33.7,36.7)	29.5 (26.6,32.5)	30.7 (25.6,35.7)	31.1 (25.7,36.5)	42.7 (39.9,45.5)	29.4 (24.4,34.3)	32.6 (27.2,37.9)	30.3 (22.9,37.6)	29.3 (23.9,34.7)	35.9 (30.1,41.7)	34.4 (29.2,39.5)	28.6 (24.8,32.4)
Have you been a happy person? (Question 9h)	25.3 (24.4,26.2)	25.9 (24.5,27.3)	19.5 (16.8,22.3)	26.0 (21.0,30.8)	27.6 (22.1,33.1)	30.7 (28.1,33.3)	23.3 (16.0,30.6)	24.5 (18.4,30.5)	20.5 (14.6,26.5)	26.9 (21.0,32.8)	32.4 (26.7,38.2)	25.3 (20.4,30.2)	19.5 (16.7,22.3)

Table 4.5: Percentage of individuals and corresponding 95% confidence intervals reporting mental health dysfunction among the general health population sample (OHLS) and childhood cancer survivors within the British Childhood Cancer Survivor Study, adjusting for sex and age

Abbreviations: HL: Hodgkin lymphoma, NHL: non-Hodgkin lymphoma, CNS: central nervous system, NH: non-heritable, H: heritable, STS: soft tissue sarcoma

	Age at SF-36 Completion							
	16-24		25-34		35-44		45+	
Question Statement	General Population Sample	All Survivors	General Population Sample	All Survivors	General Population Sample	All Survivors	General Population Sample	All Survivors
Cut down on the amount of time you spent on work or other activities? (Question 5a)	14.4(12.5,16.3)	12.9 (11.6,14.2)	12.1(10.7,13.4)	15.4(14.2,16.7)	12.1(10.7,13.5)	17.2(15.4,18.9)	12.8(11.6,13.9)	17.5(14.6,20.3)
Accomplished less than you would like? (Question 5b)	22.6(20.4,24.9)	19.0(17.5,20.6)	20.6(18.9,22.3)	20.8(19.5,22.2)	21.6(19.9,23.3)	23.6(21.7,25.6)	21.8(20.4,23.2)	24.9(21.7,28.1)
Didn't do work or other activities as carefully as usual?(Question 5c)	21.6(19.4,23.8)	14.8(13.5,16.2)	17.5(16.0,19.1)	16.7(15.4,17.9)	18.1(16.5,19.7)	18.1(16.3,19.9)	15.6(14.3,16.8)	18.1(15.1,21.0)
Has your physical health or emotional problems interfered with your normal social activities? (Question 6)	16.9(14.9,18.9)	16.1(14.7,17.5)	13.5(12.1,15.0)	18.9(17.6,20.2)	14.1(12.6,15.5)	20.4(18.5,22.2)	15.1(13.9,16.3)	21.8(18.7,24.9)
Has your health limited your social activities? (Question 9j)	11.2(9.6,12.9)	15.7(14.2,17.1)	11.2(9.9,12.5)	20.5(19.1,21.8)	13.4(12.0,14.8)	22.9(20.9,24.8)	15.3(14.1,16.5)	28.1(24.7,31.5)
Have you been a very nervous person? (Question 9b)	23.7(21.4,25.9)	30.7(28.9,32.5)	20.3(18.6,21.9)	29.7(28.1,31.2)	20.9(19.2,22.6)	26.8(24.8,28.8)	19.5(18.2,20.8)	27.5(24.2,30.8)
Have you felt so down in the dumps that nothing could cheer you up? (Question 9c)	21.2(19.1,23.4)	25.3(23.6,26.9)	17.6(16.0,19.2)	25.7(24.2,27.1)	18.1(16.5,19.6)	24.5(22.6,26.5)	17.6(16.3,18.9)	18.7(15.9,21.6)
Have you felt calm and peaceful? (Question 9d)	44.8(42.2,47.5)	43.2(41.3,45.1)	45.0(42.9,47.0)	46.8(45.1,48.4)	47.1(45.1,49.2)	47.7(45.4,49.9)	39.1(37.5,40.8)	43.1(39.4,46.7)
Have you felt downhearted and low? (Question 9f)	31.1(28.7,33.6)	35.1(33.3,37.0)	29.4(27.5,31.3)	36.4(34.8,38.0)	28.4(26.6,30.3)	35.7(33.5,37.9)	26.4(24.9,27.9)	34.1(30.6,37.6)
Have you been a happy person? (Question 9h)	22.0(19.8,24.2)	21.5(19.9,23.1)	24.1(22.3,25.9)	24.5(23.1,26.0)	27.1(25.2,28.9)	27.1(25.0,29.1)	26.2(24.7,27.7)	27.8(24.5,31.1)

Table 4.6: Percentage of individuals and corresponding 95% confidence intervals reporting mental health dysfunction by attained age among the general health population sample (OHLS) and childhood cancer survivors within the British Childhood Cancer Survivor Study, adjusting for sex and age

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	Yes	No
a Cut down on the amount of time you spent on work or other activities	☒1	☐2
b Accomplished less than you would like	☒1	☐2
c Did work or other activities less carefully than usual	☒1	☐2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐1	☐2	☒3	☒4	☒5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
b Have you been a very nervous person?	☒1	☒2	☒3	☒4	☐5	☐6
c Have you felt so down in the dumps that nothing could cheer you up?	☒1	☒2	☒3	☒4	☐5	☐6
d Have you felt calm and peaceful?	☐1	☐2	☐3	☒4	☒5	☒6
f Have you felt downhearted and blue?	☒1	☒2	☒3	☒4	☐5	☐6
h Have you been a happy person?	☐1	☐2	☐3	☒4	☒5	☒6
j Has your **health limited your social activities** (like visiting friends or close relatives)	☒1	☒2	☒3	☒4	☐5	☐6

*Question 9j is from the UK SF-36 Developmental Booklet Form

Figure 4.1: SF-36v1 questions assessed for mental health dysfunction (as portrayed in the questionnaire).
Checked boxes denote responses that were considered as 'reporting mental health dysfunction.'

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CHAPTER 5

STUDY 3:

Population-based long-term cause-specific mortality among 34,489 five-year survivors of childhood cancer in Great Britain

Abstract

Purpose: The recent extension of the British Childhood Cancer Survivor Study (BCCSS) to include five-year survivors of childhood cancer diagnosed between 1940 and 2006 provides an opportunity to investigate risk of death in relation to era of treatment, and, in particular, to address whether more modern treatments are associated with net increased or decreased risk of death from neoplastic and non-neoplastic causes.

Material and Methods: The BCCSS is a population-based cohort of 34,489 five-year survivors of childhood cancer diagnosed between 1940-2006 before the age of 15 in Britain, and to date is the largest cohort to assess late mortality. Standardized mortality ratios (SMRs) and absolute excess risks (AERs) were investigated for all deaths.

Results: Overall, 4,483 deaths were observed, which was 9.1-times the number expected. The SMR declined significantly with increasing attained age, but significant excess mortality remained even after age 65 (AER: 139.4;95%CI: 41.2-237.6). All types of childhood cancer, except non-heritable retinoblastoma, had increased mortality relative to that expected, with the greatest SMRs observed among CNS and leukemia survivors. With respect to cause-specific deaths, survivors were 27.0-times and 2.9-times more at risk of neoplastic and non-neoplastic death than expected, respectively. As attained age increased, the AERs significantly decreased for neoplastic causes and significantly increased for non-neoplastic causes (both Ptrend<0.0001). Both neoplastic and non-neoplastic AERs significantly decreased with more recent treatment decades (both Ptrend<0.0001); specifically, the neoplastic and non-neoplastic AERs in those

treated from 1990-2006 were less than a third and half of that observed in those treated before 1970 after multivariate adjustment, respectively.

Conclusions: Among five-year British survivors of childhood cancer, this study shows that the net effect of more modern treatment, screening and treatment of late effects, and supportive care is to reduce the excess numbers of both neoplastic and non-neoplastic deaths observed among five-year survivors.

Introduction

Over the past several decades, five-year survival rates from childhood cancer have increased significantly due to improvements in treatment therapies. Nonetheless, long-term survivors of childhood cancer remain at an increased risk of mortality compared to that expected[1–6]. Previous reports on late mortality have shown that the principal cause of excess mortality in the short-term is due to progression or recurrence of the initial cancer[1–3,7]. However, as follow-up increases, studies have shown that a shift occurs where subsequent primary neoplasm and non-neoplastic causes account for the majority of excess deaths among survivors later[1,2,5].

Nonetheless, it remains unclear the extent to which cause-specific mortality subsequent to five-year survival has changed following treatment in more recent eras, where increasingly therapeutic intensity has been guided by risk stratification. On one hand, treatment intensity has typically decreased for survivors diagnosed with a relatively good prognosis neoplasms in order to prevent premature morbidity and mortality from treatment related side-effects. On the other hand, treatment regimens have intensified for neoplasms with poor prognosis in order to improve five-year survival rates. Although previous studies have aimed to address late mortality across time periods[1,4,7,8], previous investigations have been restricted due to limited treatment era timespans, low person-years at risk, or relatively small numbers of deaths, which limited statistical power and inhibited detailed classification and investigation of cause-specific deaths.

In this study we aimed to address these previous limitations by investigating the risk of late cause-specific mortality following treatment across almost seven decades (1940-2006) within the recently extended British Childhood Cancer Survivor Study (BCCSS) cohort. The main

objective of this study was to determine whether excess late mortality declined for neoplastic and non-neoplastic deaths among those treated more recently. Non-neoplastic deaths were investigated overall and for specific causes including circulatory and respiratory. This current study includes an additional 7,846, 12,505, and 14,006 five-year survivors than that included in previous studies investigating late mortality from SEER[7], the CCSS[1], and Nordic countries[3], respectively; additionally, due to fact that our cohort was substantially larger than previous studies, we also observed 1,662, 2,159, and 2,407 more deaths than that reported previously by SEER[7], the CCSS[1], and Nordic countries[3], respectively. Thus, this is the largest population-based study to date to comprehensively examine late mortality and address whether more recent treatment eras are associated with a net increased or decreased risk of death.

Material and Methods

British Childhood Cancer Survivor Study

The BCCSS is the largest population-based cohort to date to comprehensively examine the late effects of childhood cancer and its treatment in relation to mortality. The cohort comprises 34,489 five-year survivors of childhood cancer diagnosed under the age of 15 years from 1940-2006 in Britain. The cohort was identified using the National Registry of Childhood Tumors, which has a high estimated level of ascertainment (~99%)[9]. Ethical approval for the study was obtained from the National Research Ethics Committee and Confidentiality Advisory Group.

Death Ascertainment

In order to ascertain each survivor's vital and embarkation status, the entire BCCSS cohort was linked to the Health and Social Care Information Centre, which includes the national population-based death registration system. An attempt was then made for each death to obtain the death certificate and underlying cause-of-death as coded by the Office of National Statistics (England and Wales) and General Registrar Office (Scotland) using the relevant *International Classification of Diseases* (ICD) used at time of death. These ICD codes were also used to classify the underlying causes-of-death by using the principal chapters of the relevant ICD revision. Follow-up for mortality commenced at the date of five-year survival and continued until the first instance of emigration, death, or February 28, 2014.

Statistical Analyses

Standardized mortality ratios (SMRs) and absolute excess risks (AERs) were calculated using standard cohort techniques[10]. The SMR was defined as the ratio of the observed over expected

number of deaths. The AER was defined as the observed minus the expected number of deaths divided by person-years at risk multiplied by 10,000. Expected numbers were calculated by multiplying the person-years for each sex-specific, age-specific (five-year bands), and calendar year-specific (one-year bands) stratum by the corresponding mortality rate for the population of England and Wales and then summing the expected numbers across the strata[11]. SMRs are useful in determining the multiplicative excess risk, whereas the AER is an additive measure for calculating the excess number of deaths in survivors compared to the background mortality per 10,000 person-years. In order to test for heterogeneity or trend in SMRs or AERs, likelihood-ratio tests within Poisson regression models were used[10]. Multivariable Poisson regression models for the SMRs and AERs were used to evaluate the simultaneous effect of the following demographic- and cancer-related factors: sex, first primary neoplasm (FPN) type, age at cancer diagnosis (0-4, 5-9, 10-14 years), treatment era (<1970, 1970-1979, 1980-1989, 1990-2006), and attained age (5-19, 20-29, 30-39, 40-49, 50-59, 60+ years).

Cumulative mortality, as a function of follow-up (years since diagnosis), was estimated by using the stcompet command in Stata[12]. Causes-of-death other than the one under study were treated as competing risks[13].

All analyses were completed using Stata 12.1 statistical software[12] where the criterion for statistical significance was a two-sided *P*-value less than 0.05.

Results

Study Characteristics

The cohort was followed up for a total of 620,758 person-years, with a mean follow-up of 18.0 (range:0.0-68.7) years from five-year survival and to a mean attained age of 29.6 (range:5.5-85.6) years. When assessed by follow-up, 57,979 and 15,835 person-years were observed beyond 35 and 45 years, respectively. With regards to attained age, 41,527 person-years were observed beyond age 45 years. Survivors of central nervous system (CNS) tumors, including primitive neuroectodermal tumors (PNET), and leukemia, including acute myeloid leukemia (AML), accounted for over 50% of the cohort. Of the 34,489 survivors, 4,483 (13.0%) had died by the study exit date (**Table 5.1**). Death certifications were obtained for 4,460 of 4,483 (99.5%) of survivors. In order to determine the cause-of-death for individuals without a death certificate, all medical information available was assessed manually to determine the likely cause; all transpired to be due to neoplastic causes.

All Causes-of-Death

Overall, survivors experienced 9.1-times (95%CI:8.9-9.4) more deaths than that expected from the general population, which equated to 64.3 (95%CI:62.2-66.4) excess deaths per 10,000 person-years (**Table 5.2**). The risk was substantially raised (SMR>10.0) for survivors of CNS PNET (SMR:23.3), leukemia (excluding AML) (SMR:15.5), AML (SMR:13.2), and CNS (excluding PNET) (SMR:11.6) (**Table 5.3**). With regards to AERs, over 50 excess deaths were observed for survivors of CNS (excluding PNET), CNS PNET, leukemia (excluding AML), AML, Hodgkin lymphoma (HL), heritable retinoblastoma, bone sarcoma, and soft tissue sarcoma. The SMR significantly decreased as follow-up (Ptrend<0.0001) and attained age

(*P*trend<0.0001) increased. Nonetheless, significant excess mortality remained even beyond age 60, where 108.1 (95%CI:63.7-152.5) excess deaths were observed. When assessed by treatment era, the SMRs and AERs decreased significantly (both *P*trend<0.0001) among those diagnosed more recently. After adjusting for sex, FPN type, age at diagnosis, and attained age, individuals diagnosed from 1990-2006 experienced 30% (EMR:0.3,95%CI:0.3-0.4) of the excess deaths observed among those diagnosed before 1970 (**Table 5.4, Figure 5.1**). When treatment era was further assessed, a statistically significant decline in excess mortality among those diagnosed more recently was observed for the following FPN types, after adjusting for sex, age at diagnosis, and attained age: CNS (excluding PNET) (*P*trend<0.0001), CNS PNET (*P*trend<0.0001), leukemia (excluding AML) (*P*trend<0.0001), AML (*P*trend=0.0279), HL (*P*trend<0.0001), non-Hodgkin lymphoma (NHL) (*P*trend=0.0257), heritable retinoblastoma (*P*trend=0.0399), and other FPN types (individuals who did not confirm to one of the finer categories of interest) (*P*trend=0.0001) (**Table 5.5**). The greatest decrease in excess risk was observed for survivors of leukemia (excluding AML) and HL, where survivors diagnosed in 1990-2006 experienced 92% and 91% less excess deaths than those diagnosed before 1970, respectively, after adjustment. A decrease in excess deaths among Wilms survivors was also observed, but the trend was slightly above that deemed as statistical significance (*P*trend=0.0509).

Further investigations into cause-specific mortality were conducted for all causes-of-death with at least 150 observed events, which were as follows: neoplastic causes overall, non-neoplastic causes overall, circulatory causes, respiratory cases, and external causes.

Cause-Specific Mortality

The SMR was significantly increased for all causes-of-death, except for deaths due to a mental disorder (**Table 5.2**). Substantial excesses in mortality (SMR>5.0) were observed for neoplastic-, stroke-, respiratory-, infection-, genitourinary-, musculoskeletal-, and blood-related deaths. The mortality was greatest for neoplastic causes at 27.0-fold (95%CI:26.1-27.9) that expected, which accounted for 82.7% of the excess deaths among survivors. Circulatory and respiratory causes-of-death were the next largest contributors for excess deaths, accounting for 9.2% of the excess when combined. When assessed by attained age, neoplastic causes-of-death accounted for the majority of excess mortality until approximately 60 years age, at which point non-neoplastic causes were the majority (**Table 5.6**); the percentage of excess deaths attributable to non-neoplastic causes rose rapidly with attained age from 7.7% among those aged 5-19 years to 53.0% among those aged beyond 60 years. The proportion of excess death due to circulatory causes also increased with attained age; the largest proportion of excess mortality among those aged beyond 60 years was due to circulatory causes, accounting for 36.8% of the total excess mortality and 69.4% of the excess non-neoplastic mortality. The proportion of excess death due to respiratory causes also increased with attained age.

Neoplastic Causes-of-Death

There were 3,427 neoplastic deaths observed in the cohort, accounting for 76.4% of the deaths (**Table 5.3**). All FPN types were at a statistically significant increased risk of premature neoplastic death, where the SMR ranged from 2.2-fold in survivors of non-heritable retinoblastoma to 152.2-fold in survivors of CNS PNET. As follow-up and attained age increased, the SMR significantly declined (both *P*trend<0.0001). From age 5-19 to beyond age

60 the SMR declined from 200.0 (95%CI:191.3-208.9) to 2.1 (95%CI:1.5-2.8), respectively. Nonetheless, over 50 (AER:50.8,95%CI:20.6-81.1) excess neoplastic deaths were observed beyond age 60. With regards to treatment era, the AER significantly decreased among those treated more recently (*P*trend<0.0001) (**Table 5.4, Figure 5.1**). Compared to survivors diagnosed before 1970, those diagnosed between 1990-2006 experienced 30% (EMR:0.3,95%CI:0.3-0.4) of the excess neoplastic deaths, after adjusting for sex, FPN type, age at diagnosis, and attained age (**Table 5.3**). When treatment era was assessed by FPN type, survivors of CNS (excluding PNET) (*P*trend<0.0001), CNS PNET (*P*trend<0.0001), leukemia (excluding AML) (*P*trend<0.0001), AML (*P*trend=0.0035), HL (*P*trend<0.0001), NHL (*P*trend=0.0411), and other FPN types (*P*trend<0.0001) were found to have significantly less excess mortality among those diagnosed most recently (**Table 5.5**). Again, this decrease was greatest for leukemia (excluding AML) and HL survivors who were both found to have 93% less excess deaths in those diagnosed between 1990-2006 compared to those diagnosed before 1970. Nonetheless, all FPN types reporting a significant trend with treatment era were found to have an EMR of at least 0.6 for those diagnosed from 1990-2006, which equated to approximately a 40% decrease in excess risk among those diagnosed from 1990-2006 compared to those diagnosed before 1970.

Non-Neoplastic Causes-of-Death

Survivors of childhood cancer were 2.9-times (95%CI:2.7-3.1) more likely to die from a non-neoplastic cause-of-death than expected in the general population, which equated to 11.1 (95%CI:10.1-12.2) excess non-neoplastic deaths per 10,000 person-years (**Table 5.3**). Survivors of AML, CNS PNET, and CNS (excluding PNET) were at greatest risk of non-neoplastic death

with SMRs of 5.1 (95%CI:3.3-7.5), 4.7 (95%CI:3.5-6.2), and 4.6 (95%CI:4.1-5.1), respectively. Survivors of non-heritable retinoblastoma, heritable retinoblastoma, and bone sarcoma were not found to be at a significantly increased risk of non-neoplastic death. The SMR was not observed to have significant heterogeneity or trend as follow-up increased (both $P>0.05$), although the AER did significantly increase as follow-up increased (Ptrend<0.0001). The SMR declined (Ptrend=0.0040) and the AER increased (Ptrend<0.0001) significantly as attained age increased, with 57.3 (95%CI:24.8-89.7) excess non-neoplastic deaths occurring beyond age 60. The number of excess non-neoplastic deaths among survivors was also observed to decrease with more recent treatment eras (Ptrend=0.0016) (**Table 5.4, Figure 5.1**); survivors diagnosed between 1990-2006 experienced 60% (EMR:0.6,95%CI:0.4-0.8) of the excess numbers of non-neoplastic deaths than observed among survivors diagnosed before 1970. When treatment era was further assessed by FPN type, only CNS (excluding PNET) (Ptrend=0.0229) and HL (Ptrend=0.0237) survivors were found to have a significant decrease in excess non-neoplastic mortality among those treated more recently (**Table 5.5**). Fifty percent (EMR:0.5,95%CI:0.3-0.9) of the excess number of deaths from non-neoplastic causes was observed among CNS (excluding PNET) survivors diagnosed from 1990-2006 compared to those diagnosed before 1970, whilst the corresponding figure among HL survivors was 30% (EMR:0.3,95%CI:0.1-1.1). Decreases in excess non-neoplastic deaths were also observed for NHL and neuroblastoma survivors, but these were not statistically significant (both Ptrend>0.05), likely due to decreased statistical power.

Circulatory Causes-of-Death

In absolute terms, circulatory causes accounted for the largest proportion of non-neoplastic deaths with 302 observed events (**Table 5.3**). Survivors were 3.9-times (95%CI:3.4-4.3) more at risk of circulatory death than expected, which equated to 3.6 (95%CI:3.1-4.2) excess circulatory deaths per 10,000 person-years. The risk of circulatory death was substantially raised (SMR>5.0) for survivors of AML (SMR:16.6), CNS PNET (SMR:6.8), Wilms (SMR:5.8), and HL (SMR:5.1). As follow-up since diagnosis increased, the SMRs significantly decreased (*P*trend=0.0011) and AER significantly increased (*P*trend<0.0001). Similarly, the SMRs significantly decreased (*P*trend=0.0002) and AERs significantly increased (*P*trend<0.0001) as attained age increased; even after 60 years age the SMR was significantly elevated at 2.4 (95%CI:1.6-3.5), which equated to 39.8 (95%CI:14.8-64.8) excess circulatory deaths per 10,000 person-years. Although a significant decline was observed when assessing the cumulative mortality of circulatory deaths by treatment era (**Figure 5.1**), no effect for treatment era was found in the multivariate Poisson model (*P*trend=0.1572), which took into account the expected rates of circulatory death and adjusted for sex, FPN type, age at diagnosis, and attained age (**Table 5.4**).

Respiratory Causes-of-Death

Respiratory-related deaths were the second largest cause of non-neoplastic death with 164 observed events, which was 6.8-times (95%CI:5.8-7.9) that expected from the general population (**Table 5.3**). A substantial excess risk (SMR>5) was observed among survivors of CNS PNET (SMR:22.6), AML (SMR:12.6), CNS (excluding PNET) (SMR:11.9), leukemia (excluding AML) (SMR:8.5), neuroblastoma (SMR:7.2), and soft tissue sarcoma (SMR:5.4). The SMRs significantly declined (*P*trend=0.0049) and the AER significantly increased (*P*trend=0.0006) as

follow-up increased. Similarly, the SMR significantly declined (*P*trend=0.0001) and AER significantly increased (*P*trend=0.0386) with attained age. When treatment era was assessed, a statistically significant decline (*P*trend=0.0127) in excess mortality was observed among those treated more recently, after adjusting for sex, FPN type, age at diagnosis, and attained age (**Table 5.4, Figure 1**); compared to survivors diagnosed before 1970, survivors diagnosed from 1990-2006 experienced 40% (EMR:0.6,95%CI:0.2-1.4) less excess respiratory deaths.

External Causes-of-Death

Survivors of childhood cancer had a slight increased risk of death due to external causes compared to that expected with an SMR of 1.2 (95%CI:1.1-1.4) (**Table 5.3**). Only survivors of CNS (excluding PNET) (SMR:2.0,95%CI:1.5-2.6) and neuroblastoma (SMR:2.2,95%CI:1.1-3.9) had a significant increased risk compared to that expected. The SMRs and AERs were not found to vary across follow-up nor attained age (all *P*heterogeneity>0.05 *&* all *P*trend>0.05), suggesting the risk of death due to external causes was constant throughout follow-up and the lifespan. With regards to treatment era, the number of excess deaths due to external causes significantly declined among those treated more recently (**Table 5.3, Figure 1**).

Discussion

Due to our study's wide period of diagnosis, long follow-up time, large number of observed events, and population-based design, this is the first study to comprehensively investigate late mortality among five-year childhood cancer survivors beyond 50 years age, whilst also assessing treatment era effects in cause-specific mortality. Previously we have reported the risk of cause-specific death after childhood cancer within the same cohort[2]. However, this updated analysis includes an additional 16,509 survivors and adds a further 1,434 deaths and 250,733 person-years, ultimately providing more precise risk estimates of late mortality among childhood cancer survivors. Furthermore, this study additionally expands upon previous findings from the Childhood Cancer Survivor Study (CCSS)[1], Surveillance, Epidemiology and End Results Program (SEER)[7], and the Nordic countries[3], by including a further 7,846, 12,505, and 14,006 five-year survivors and 2,407, 2,159, and 1,662 deaths, respectively.

The findings from our study support that the net effect of more modern treatment, increased screening and treatment of late effects, and improved supportive care, which was available for survivors more recently diagnosed, was to reduce excess mortality for all, neoplastic, non-neoplastic, respiratory, and external causes. These findings complement previous literature that has suggested that late mortality was higher in earlier treatment eras (before 1970) than in more recent times (1970 to present), a period where multimodal therapy has been available, among five-year survivors of childhood cancer[14–17]. Three previous large cohorts from SEER[7], the Nordic countries[3], and the CCSS [1] have reported on treatment era effects among childhood cancer survivors. In the first publication, SEER assessed survivors diagnosed from 1974-2000 and reported that all cause late mortality improved among those treated more recently, largely due to

a reduction of excess deaths attributable to recurrence/progression of the original cancer[7]. Similarly, the Nordic cohort, which assessed five-year survivors diagnosed from 1960-1989, found that the cumulative mortality from all causes, recurrence/progression of the primary cancer, and other causes excluding subsequent cancers declined significantly among those more recently treated (all $P<0.001$)[3]. Finally, the CCSS found that among 20,483 survivors (2,821 deaths), the mortality rate remained stable over the treatment period of 1970-1986[1]. Our findings complement the SEER and Nordic studies, as well as smaller reports that investigated treatment era trends in Scotland[4] and British Columbia, Canada[8], as we too found a decline in excess mortality for all causes and neoplastic-related deaths; however, this study also further expands upon the knowledge in the field of treatment era effects among childhood cancer survivors as we have identified significant decreases in excess mortality for non-neoplastic causes overall, respiratory causes, and external causes, after taking into account the background expected risks and potential confounders.

This study also illustrates treatment era effects by each FPN type for all causes-of-death. To our knowledge, only one other study by SEER has assessed treatment era by FPN[7]; in this study, significant declines ($P<0.05$) in ten-year all cause cumulative mortality was observed for survivors of all leukemias, acute lymphoblastic leukemia, HL, NHL, Ewing sarcoma, and rhabdoymosarcoma[7]. These findings broadly correspond with our study as we too found significant declines with treatment era for leukemia (excluding AML), AML, HL, and NHL when assessing all cause mortality via multivariate Poisson models. However, our finding build upon the Armstrong et al. study by additionally finding significant declines in excess all cause mortality for CNS (excluding PNET), CNS PNET, heritable retinoblastoma, and other FPNs. A

potential explanation for the differences between our studies may be the fact that the SEER study investigated treatment era effects for the diagnosis period of 1974-2000, whilst our study included diagnoses from 1940-2006. Due to our wide diagnosis period, we were able to compare multimodal treatment eras to pre-chemotherapy (1940-1959) and first-generation chemotherapy (1960-1974) eras, whereas the SEER study covers a diagnosis period where multimodal treatment was generally available for all survivors. Thus, as our study spans a diagnosis period with more variable treatment regimens, it is expected that we would be able to better discern decreases in excess mortality as substantial improvements in treatment and care have occurred from the 1940s to 1970s.

Furthermore, this is the first study to our knowledge to illustrate significant declines in excess mortality by treatment era for both neoplastic and non-neoplastic causes for some FPN types. Previously, SEER reported significant declines in cumulative mortality for recurrence/progression of the primary cancer for some FPN types, but was unable to identify significant declines in non-recurrence non-external deaths among survivors more recently diagnosed [7]. Our study, however, was able to identify significant declines in neoplastic deaths for CNS (excluding PNET), CNS PNET, leukemia (excluding AML), AML, HL, NHL, and other FPNs. Survivors of CNS (excluding PNET) and HL were also found to have significantly less excess non-neoplastic deaths among individuals diagnosed more recently. Although chemotherapy generally is not used to treat CNS (excluding PNET) tumors, increased precision in the removal and resection of the tumor, smaller and more accurate radiotherapy fields, risk-stratified driven levels of radiotherapy exposure, and increased awareness of adverse late effects have likely contributed to the significant decline in excess neoplastic and non-neoplastic

mortality. Chemotherapy has, however, played an important role in survivors of CNS PNET; based upon the findings of the UK PNET-3 trial, survivors treated with surgery, chemotherapy, then radiotherapy have been found to have improved event-free and overall survival compared to individuals treated with only surgery and radiotherapy[18]. This trial highlights the importance of removing as much of the tumors as possible and further treating any residual tumor cells with chemotherapy and radiotherapy[18]; this, in addition to improved surgical precision, may have led to decreased neoplastic mortality among CNS PNET survivors more recently diagnosed. For leukemia survivors, a large decline in excess mortality was observed from 1970-1979 where, compared to individuals diagnosed before 1970, the excess mortality decreased by 40% (EMR:0.6); this finding likely corresponds with the introduction of combination chemotherapy, which was introduced in the early 1970s and intensified during the 1980s[19]. Further reductions in excess neoplastic mortality may also relate to radiotherapy use, as CNS irradiation to treat leukemia was diminished by the late 1980s, reducing the risk of treatment-induced subsequent cancers[20,21]. A key factor associated with improved prognosis for AML survivors was the relatively recent identification of cytogenetics, which have been shown through the Medical Research Council AML 10 trial to be useful for providing the framework for a stratified treatment approach[22]; this approach may have in return decreased excess neoplastic mortality by reducing the likelihood of a relapse occurring, which to date still has a poor prognosis. With regards to HL survivors, multimodal therapy with reduced radiation doses among individuals more recently diagnosed likely contributed to the large decrease in excess mortality during the diagnosis period of 1970-1979 period where, compared to those treated before 1970, a 60% (EMR:0.4) decrease in excess mortality was observed. Further decreases in excess mortality among those diagnosed from 1980-1989 and 1990-2006 may be associated with lower cumulative doses of anthracyclines

to reduce cardiotoxicity and increased awareness and screening of late adverse effects[7,23–25]. Finally, prior to the 1970s, few children survived NHL[26]. However, in the mid-1970s, reports began to appear suggesting improved survival and outcomes due to intensive regimens including multiple chemotherapy drugs, irradiation to involved fields, and prophylactic treatment of the CNS[26]. Treatment intensity of NHL then subsequently decreased for individuals with a good prognosis, in order to reduce acute toxicities and late adverse effects, and intensified among individuals with a poor prognosis[26]. These treatment changes over time for NHL survivors increased five-year survival from a largely fatal disease and likely contributed to the significant decline in excess neoplastic deaths.

And, finally, this study expands upon our previous work on late mortality by extending the mortality analysis to beyond 60 years follow-up[2]. In doing so, we identified a persistence of excess death even beyond 50 years age, suggesting that childhood cancer survivors will likely remain at an elevated risk of premature mortality for the majority, if not entirety, of their lifespan. Although neoplastic-related deaths were the principal cause of excess mortality overall, excess non-neoplastic deaths increased rapidly with attained age, ultimately becoming the more prominent concern among older survivors. Excess non-neoplastic mortality is likely attributable to late complications of treatment, as radiotherapy and chemotherapy have been associated with adverse circulatory[27–31], respiratory[32–34], endocrine[35,36], neurologic[37–39], and other chronic health conditions[35,40]. Although the change in the proportion of excess deaths attributable to neoplastic causes with extending follow-up or attained age is not new, with our previous study[2] and the CCSS reporting the same transition towards non-neoplastic causes[1,41], this is the first study to satisfactorily assess late mortality among a population of childhood cancer survivors in their fifth

and sixth decades of life. In doing so, this study provides the initial findings for late mortality among childhood cancer survivors who have reached late adulthood. These results will be useful for informing older survivors and clinicians about the persisting increased risks of premature mortality, despite the many decades that may have passed since the original childhood cancer diagnosis. Additionally, our results will also serve as a predictor of the future changes and trends of late mortality that may occur with on-going follow-up as this population of childhood cancer survivors reaches elderly age.

Limitations

A limitation of our study is the high level of missing treatment information, which prohibited any examination of patterns of treatment exposures in relation to cause specific mortality risk. Another possible limitation of this study is that our classification of deaths relied upon the underlying cause-of-death as coded on the death certificate. Death certificates have been previously shown to have imperfect accuracy in regards to the cause-of-death, and thus some degree of misclassification is inherent in our data[42–45]. Nonetheless, it is more likely that we have under-ascertained non-neoplastic deaths, which were largely the outcomes of interest for the cause-specific analysis in this study, as childhood cancer survivors are more likely to be coded as having a neoplastic-related death due to their previous medical history[46]. Thus, our results likely underestimated the risk of non-neoplastic deaths among survivors of childhood cancer, and in doing so should still be useful for identifying individuals with increased risks of premature mortality.

Conclusions

In conclusion, the findings from this large-scale, population-based study provide evidence that excess deaths among five-year British survivors of childhood cancer increase significantly with attained age, with a substantial number of survivors dying prematurely even beyond 50 years age. Nonetheless, there is evidence that the net effect of more modern treatments, screening and detection of late effects, and improvements in supportive care translates into a reduction in the excess numbers of both neoplastic and non-neoplastic deaths among five-year survivors. These findings provide unbiased and reliable estimates of late mortality among childhood cancer survivors, which will be useful for informing clinicians and survivors regarding the increased risk of premature mortality.

Patient Characteristic	Dead	%	Alive	%	Total	%
Overall	4,483	13.0	30,006	87.0	34,489	100.0
Sex						
Male	2,635	13.9	16,304	86.1	18,939	100.0
Female	1,848	11.9	13,702	88.1	15,550	100.0
First Primary Neoplasm Type						
CNS (excluding PNET)	1,335	19.2	5,634	80.8	6,970	100.0
CNS PNET	341	28.5	857	71.5	1,198	100.0
Leukemia (excluding AML)	1,103	11.6	8,390	88.4	9,493	100.0
AML	82	8.4	899	91.6	981	100.0
Hodgkin Lymphoma	335	15.0	1,899	85.0	2,234	100.0
Non-Hodgkin Lymphoma	131	8.5	1,418	91.5	1,549	100.0
Neuroblastoma	144	9.4	1,391	90.6	1,535	100.0
Non-Heritable Retinoblastoma	31	3.1	975	96.9	1,006	100.0
Heritable Retinoblastoma	139	18.5	611	81.5	750	100.0
Wilms	184	7.7	2,204	92.3	2,388	100.0
Bone Sarcoma	198	16.6	997	83.4	1,195	100.0
Soft Tissue Sarcoma	253	11.8	1,894	88.2	2,147	100.0
Other	206	6.8	2,837	93.2	3,043	100.0
Age at Diagnosis						
0-4	1,662	10.6	14,035	89.4	15,697	100.0
5-9	1,355	14.6	7,909	85.4	9,264	100.0
10-14	1,466	15.4	8,062	84.6	9,528	100.0
Treatment Era						
1940-1969	1,333	35.6	2,413	64.4	3,746	100.0
1970-1979	1,251	23.3	4,128	76.7	5,379	100.0
1980-1989	941	13.2	6,206	86.8	7,147	100.0
1990-1999	703	7.0	9,328	93.0	10,031	100.0
2000-2006	255	3.1	7,931	96.9	8,186	100.0
Years Follow-Up						
Mean (SD)	12	13.3	18.9	12.5	18	12.8
5-9	2,720	23.4	8,921	76.6	11,641	100.0
10-19	699	7.2	9,047	92.8	9,746	100.0
20-29	491	7.5	6,049	92.5	6,540	100.0
30-39	325	7.8	3,830	92.2	4,155	100.0
40-49	209	11.3	1,642	88.7	1,851	100.0
50-59	34	6.5	490	93.5	524	100.0
60+	5	15.6	27	84.4	32	100.0
Attained Age						
Mean (SD)	24.3	13.8	30.4	13.1	29.6	13.4
5-9	416	48.9	435	51.1	851	100.0
10-19	1,834	21.7	6,611	78.3	8,445	100.0
20-29	1,005	9.4	9,728	90.6	10,733	100.0
30-39	536	8.1	6,082	91.9	6,618	100.0
40-49	366	7.5	4,484	92.5	4,850	100.0
50-59	238	11.3	1,859	88.7	2,097	100.0
60+	88	9.8	807	90.2	895	100.0

Table 5.1: Cohort characteristics of the British Childhood Cancer Survivor Study

Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia

	O/E	SMR (95%CI)	AER (95%CI)
All Causes	4483/490.9	9.1 (8.9,9.4)	64.3 (62.2,66.4)
Neoplastic	3427/126.9	27.0 (26.1,27.9)	53.2 (51.3,55.0)
Non-Neoplastic	1056/364.0	2.9 (2.7,3.1)	11.1 (10.1,12.2)
Circulatory	302/78.0	3.9 (3.4,4.3)	3.6 (3.1,4.2)
Cardiac	182/53.1	3.4 (2.9,4.0)	2.1 (1.6,2.5)
Stroke	78/15.2	5.1 (4.1,6.4)	1.0 (0.7,1.3)
Respiratory	164/24.2	6.8 (5.8,7.9)	2.3 (1.8,2.7)
Nervous	98/23.0	4.3 (3.5,5.2)	1.2 (0.9,1.5)
Infection	67/9.1	7.4 (5.7,9.4)	0.9 (0.7,1.2)
Digestive	63/30.6	2.1 (1.6,2.6)	0.5 (0.3,0.8)
Perinatal	42/9.5	4.4 (3.2,6.0)	0.5 (0.3,0.7)
Endocrine	32/10.5	3.1 (2.1,4.3)	0.3 (0.2,0.5)
Genitourinary	30/3.3	9.2 (6.2,13.2)	0.4 (0.3,0.6)
Musculoskeletal	18/3.0	6.0 (3.5,9.4)	0.2 (0.1,0.4)
Mental	15/13.3	1.1 (0.6,1.9)	0.0 (-0.1,0.1)
Blood	16/2.1	7.5 (4.3,12.2)	0.2 (0.1,0.3)
External	188/151.7	1.2 (1.1,1.4)	0.6 (0.2,1.0)
Other	21/5.7	3.7 (2.3,5.7)	0.2 (0.1,0.4)

Table 5.2: Observed and expected deaths, standardized mortality ratio, and absolute excess risk of specific causes-of-death
Abbreviation: O: observed; E: expected; SMR: standardized mortality ratio; CI: confidence interval; AER: absolute excess risk

		All Causes			Neoplastic Causes			Non-Neoplastic Causes		
	Person-Years	**O/E**	**SMR (95%CI)**	**AER (95%CI)**	**O/E**	**SMR (95%CI)**	**AER (95%CI)**	**O/E**	**SMR (95%CI)**	**AER (95%CI)**
Overall	620,758	4483/490.9	9.1 (8.9,9.4)	64.3 (62.2,66.4)	3427/126.9	27.0 (26.1,27.9)	53.2 (51.3,55.0)	1056/364.0	2.9 (2.7,3.1)	11.1 (10.1,12.2)
Sex										
Male	336,802	2635/332.7	7.9 (7.6,8.2)	68.4 (65.4,71.3)	1995/66.6	30.0 (28.7,31.3)	57.3 (54.7,59.9)	640/266.1	2.4 (2.2,2.6)	11.1 (9.6,12.6)
Female	283,955	1848/158.3	11.7 (11.1,12.2)	59.5 (56.5,62.5)	1432/60.3	23.7 (22.5,25.0)	48.3 (45.7,50.9)	416/97.9	4.2 (3.8,4.7)	11.2 (9.8,12.6)
*P*heterogeneity			<0.0001[a]	0.0004[a]		0.2999[a]	<0.0001[a]		<0.0001[a]	0.8155[a]
First Primary Neoplasm Type										
CNS (excluding PNET)	124,750	1336/115.5	11.6 (11.0,12.2)	97.8 (92.1,103.6)	957/32.7	29.3 (27.5,31.2)	74.1 (69.2,79.0)	379/82.9	4.6 (4.1,5.1)	23.7 (20.7,26.8)
CNS PNET	18,699	341/14.6	23.3 (20.9,26.0)	174.6 (155.2,193.9)	288/3.3	86.3 (76.6,96.8)	152.2 (134.4,170.0)	53/11.3	4.7 (3.5,6.2)	22.3 (14.7,29.9)
Leukemia (excluding AML)	145,237	1103/71.2	15.5 (14.6,16.4)	71.0 (66.6,75.5)	955/12.7	75.1 (70.4,80.0)	64.9 (60.7,69.0)	148/58.5	2.5 (2.1,3.0)	6.2 (4.5,7.8)
AML	13,029	82/6.2	13.2 (10.5,16.4)	58.2 (44.5,71.8)	56/1.1	50.7 (38.3,65.8)	42.1 (30.9,53.4)	26/5.1	5.1 (3.3,7.5)	16.0 (8.4,23.7)
Hodgkin Lymphoma	42,600	335/47.3	7.1 (6.3,7.9)	67.5 (59.1,75.9)	243/11.5	21.1 (18.5,23.9)	54.3 (47.2,61.5)	92/35.8	2.6 (2.1,3.2)	13.2 (8.8,17.6)
Non-Hodgkin Lymphoma	30,343	131/31.9	4.1 (3.4,4.9)	32.7 (25.3,40.1)	79/8.2	9.7 (7.6,12.0)	23.3 (17.6,29.1)	52/23.7	2.2 (1.6,2.9)	9.3 (4.7,14.0)
Neuroblastoma	28,500	144/16.8	8.5 (7.2,10.1)	44.6 (36.4,52.9)	107/4.2	25.7 (21.1,31.1)	36.1 (29.0,43.2)	37/12.7	2.9 (2.1,4.0)	8.5 (4.3,12.7)
Non-Heritable Retinoblastoma	26,167	31/23.2	1.3 (0.9,1.9)	3.0 (-1.2,7.2)	15/6.8	2.2 (1.2,3.6)	3.1 (0.2,6.0)	16/16.4	1.0 (0.6,1.6)	, 0.1 (-3.1,2.9)
Heritable Retinoblastoma	20,162	139/16.9	8.2 (6.9,9.7)	60.6 (49.1,72.0)	121/4.7	25.6 (21.3,30.6)	57.7 (47.0,68.4)	18/12.2	1.5 (0.9,2.3)	2.9 (-1.2,7.0)
Wilms	51,519	184/33.8	5.4 (4.7,6.3)	29.1 (24.0,34.3)	101/8.1	12.5 (10.2,15.1)	18.0 (14.2,21.9)	83/25.7	3.2 (2.6,4.0)	11.1 (7.6,14.6)
Bone Sarcoma	21,798	198/24.6	8.0 (7.0,9.2)	79.5 (66.9,92.2)	172/7.4	23.1 (19.8,26.8)	75.5 (63.7,87.3)	26/17.2	1.5 (1.0,2.2)	4.0 (-0.5,8.6)
Soft Tissue Sarcoma	42,062	253/39.2	6.5 (5.7,7.3)	50.8 (43.4,58.2)	199/10.9	18.3 (15.8,21.0)	44.7 (38.1,51.3)	54/28.3	1.9 (1.4,2.5)	6.1 (2.7,9.5)
Other	55,891	206/49.5	4.2 (3.6,4.8)	28.0 (23.0,33.0)	134/15.2	8.8 (7.4,10.5)	21.3 (17.2,25.3)	72/34.4	2.1 (1.6,2.6)	6.7 (3.8,9.7)
*P*heterogeneity			<0.0001[a]	<0.0001[a]		<0.0001[a]	<0.0001[a]		<0.0001[a]	<0.0001[a]
Age at Diagnosis										
0-4 years	291,564	1662/167.9	9.9 (9.4,10.4)	51.2 (48.5,54.0)	1283/38.6	33.2 (31.4,35.1)	42.7 (40.3,45.1)	379/129.3	2.9 (2.6,3.2)	8.6 (7.3,9.9)
5-9 years	163,195	1355/128.6	10.5 (10.0,11.1)	75.2 (70.7,79.6)	1055/31.1	33.9 (31.9,36.1)	62.7 (58.8,66.6)	300/97.5	3.1 (2.7,3.4)	12.4 (10.3,14.5)
10-14 years	165,999	1466/194.4	7.5 (7.2,7.9)	76.6 (72.1,81.1)	1089/57.2	19.0 (17.9,20.2)	62.2 (58.3,66.1)	377/137.2	2.7 (2.5,3.0)	14.4 (12.2,16.7)
*P*heterogeneity			<0.0001[a]	<0.0001[a]		<0.0001[a]	<0.0001[a]		0.0723[a]	0.7330[a]
*P*trend			<0.0001[a]	<0.0001[a]		<0.0001[a]	<0.0001[a]		0.0307[a]	0.4311[a]

Table 5.3: Standardized mortality ratios and absolute excess risks for deaths due to all, neoplastic, non-neoplastic, circulatory, respiratory, and external causes, by potential explanatory factors

Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia, O: observed, E: expected, SMR: standardized mortality ratio, CI: confidence interval, AER: absolute excess risk

[a] *P*heterogeneity or *P*trend determined from multivariate Poisson model adjusting for sex, first primary neoplasm type, age at diagnosis, treatment era, and attained age

[b] *P*heterogeneity or *P*trend determined from multivariate Poisson model adjusting for sex, first primary neoplasm type, age at diagnosis, treatment era, and follow-up

		All Causes			Neoplastic Causes			Non-Neoplastic Causes		
	Person-Years	**O/E**	**SMR (95%CI)**	**AER (95%CI)**	**O/E**	**SMR (95%CI)**	**AER (95%CI)**	**O/E**	**SMR (95%CI)**	**AER (95%CI)**
Treatment Era										
<1970	135,884	1333/228.1	5.8 (5.5,6.2)	81.3 (76.0,86.6)	936/79.7	11.8 (11.0,12.5)	63.0 (58.6,67.4)	397/148.5	2.7 (2.4,3.0)	18.3 (15.4,21.2)
1970-1979	152,278	1251/125.0	10.0 (9.5,10.6)	73.9 (69.4,78.5)	951/26.9	35.4 (33.2,37.7)	60.7 (56.7,64.7)	300/98.1	3.1 (2.7,3.4)	13.3 (11.0,15.5)
1980-1989	155,375	941/85.0	11.1 (10.4,11.8)	55.1 (51.2,59.0)	728/13.1	55.7 (51.7,59.9)	46.0 (42.6,49.4)	213/71.9	3.0 (2.6,3.4)	9.1 (7.2,10.9)
1990-2006	177,221	958/52.9	18.1 (17.0,19.3)	51.1 (47.7,54.5)	812/7.3	110.8 (103.3,118.7)	45.4 (42.3,48.6)	146/45.5	3.2 (2.7,3.8)	5.7 (4.3,7.0)
*P*heterogeneity			<0.0001[a]	<0.0001[a]		<0.0001[a]	<0.0001[a]		0.7912[a]	0.0031[a]
*P*trend			<0.0001[a]	<0.0001[a]		<0.0001[a]	<0.0001[a]		0.7150[a]	0.0016[a]
Years Follow-Up										
5-19 years	390,711	3120/156.8	19.9 (19.2,20.6)	75.8 (73.0,78.6)	2695/21.2	126.9 (122.2,131.8)	68.4 (65.8,71.0)	425/135.5	3.1 (2.8,3.4)	7.4 (6.4,8.4)
20-29 years	132,085	547/101.7	5.4 (4.9,5.8)	33.7 (30.2,37.2)	317/19.8	16.0 (14.3,17.9)	22.5 (19.9,25.1)	230/82.0	2.8 (2.5,3.2)	11.2 (9.0,13.5)
30-39 years	66,379	420/98.9	4.2 (3.9,4.7)	48.4 (42.3,54.4)	220/29.8	7.4 (6.4,8.4)	28.6 (24.3,33.0)	200/69.1	2.9 (2.5,3.3)	19.7 (15.5,23.9)
40-49 years	24,972	277/83.5	3.3 (2.9,3.7)	77.5 (64.4,90.5)	134/33.5	4.0 (3.3,4.7)	40.2 (31.2,49.3)	143/50.0	2.9 (2.4,3.4)	37.2 (27.9,46.6)
50-59 years	6,102	103/43.0	2.4 (2.0,2.9)	98.3 (65.7,130.9)	54/19.5	2.8 (2.1,3.6)	56.5 (32.9,80.1)	49/23.5	2.1 (1.5,2.8)	41.8 (19.3,64.3)
60+ years	508	16/7.0	2.3 (1.3,3.7)	177.4 (23.0,331.9)	7/3.0	2.3 (0.9,4.8)	78.3 (-23.9,180.4)	9/4.0	2.3 (1.0,4.3)	99.1 (-16.7,215.0)
*P*heterogeneity			<0.0001[b]	<0.0001[b]		<0.0001[b]	<0.0001[b]		0.5209[b]	<0.0001[b]
*P*trend			<0.0001[b]	<0.0001[b]		<0.0001[b]	<0.0001[b]		0.2465[b]	<0.0001[b]
Attained Age										
5-19 years	243,035	2250/70.5	31.9 (30.6,33.3)	89.7 (85.9,93.5)	2022/10.1	200.0 (191.3,208.9)	82.8 (79.2,86.4)	228/60.4	3.8 (3.3,4.3)	6.9 (5.7,8.1)
20-29 years	195,584	1005/111.2	9.0 (8.5,9.6)	45.7 (42.5,48.9)	739/13.7	54.1 (50.2,58.1)	37.1 (34.4,39.8)	266/97.5	2.7 (2.4,3.1)	8.6 (7.0,10.2)
30-39 years	108,573	536/94.8	5.7 (5.2,6.2)	40.6 (36.5,44.8)	324/20.2	16.0 (14.3,17.8)	28.0 (24.7,31.2)	212/74.6	2.8 (2.5,3.3)	12.7 (10.0,15.3)
40,49 years	51,869	366/95.1	3.9 (3.5,4.3)	52.2 (45.0,59.5)	184/30.5	6.0 (5.2,7.0)	29.6 (24.5,34.7)	182/64.6	2.8 (2.4,3.3)	22.6 (17.5,27.7)
50-59 years	17,552	238/76.1	3.1 (2.7,3.6)	92.2 (75.0,109.5)	117/32.5	3.6 (3.0,4.3)	48.2 (36.1,60.2)	121/43.6	2.8 (2.3,3.3)	44.1 (31.8,56.4)
60+ years	4,144	88/43.2	2.0 (1.6,2.5)	108.1 (63.7,152.5)	41/19.9	2.1 (1.5,2.8)	50.8 (20.6,81.1)	47/23.3	2.0 (1.5,2.7)	57.3 (24.8,89.7)
*P*heterogeneity			<0.0001[a]	<0.0001[a]		<0.0001[a]	<0.0001[a]		0.0172[a]	<0.0001[a]
*P*trend			<0.0001[a]	<0.0001[a]		<0.0001[a]	<0.0001[a]		0.0040[a]	<0.0001[a]

Table 5.3 (*continued*): Standardized mortality ratios and absolute excess risks for deaths due to all, neoplastic, non-neoplastic, circulatory, respiratory, and external causes, by potential explanatory factors

Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia, O: observed, E: expected, SMR: standardized mortality ratio, CI: confidence interval, AER: absolute excess risk

[a] *P*heterogeneity or *P*trend determined from multivariate Poisson model adjusting for sex, first primary neoplasm type, age at diagnosis, treatment era, and attained age

[b] *P*heterogeneity or *P*trend determined from multivariate Poisson model adjusting for sex, first primary neoplasm type, age at diagnosis, treatment era, and follow-up

		Circulatory Causes			Respiratory Causes			External Causes		
	Person-Years	**O/E**	**SMR (95%CI)**	**AER (95%CI)**	**O/E**	**SMR (95%CI)**	**AER (95%CI)**	**O/E**	**SMR (95%CI)**	**AER (95%CI)**
Overall	620,758	302/78.0	3.9 (3.4,4.3)	3.6 (3.1,4.2)	164/24.2	6.8 (5.8,7.9)	2.3 (1.8,2.7)	188/151.7	1.2 (1.1,1.4)	0.6 (0.2,1.0)
Sex										
Male	336,802	178/56.8	3.1 (2.7,3.6)	3.6 (2.8,4.4)	98/14.9	6.6 (5.3,8.0)	2.5 (1.9,3.0)	133/122.9	1.1 (0.9,1.3)	0.3 (-0.4,1.0)
Female	283,955	124/21.2	5.9 (4.9,7.0)	3.6 (2.9,4.4)	66/9.3	7.1 (5.5,9.0)	2.0 (1.4,2.6)	55/28.8	1.9 (1.4,2.5)	0.9 (0.4,1.4)
*P*heterogeneity			<0.0001[a]	0.6211[a]		0.6059[a]	0.1717[a]		0.0013[a]	0.3063[a]
First Primary Neoplasm										
CNS (excluding PNET)	124,750	90/20.1	4.5 (3.6,5.5)	5.6 (4.1,7.1)	72/6.1	11.9 (9.3,15.0)	5.3 (4.0,6.6)	64/31.9	2.0 (1.5,2.6)	2.6 (1.3,3.8)
CNS PNET	18,699	15/2.2	6.8 (3.8,11.2)	6.8 (2.8,10.9)	15/0.7	22.6 (12.7,37.4)	7.7 (3.6,11.7)	7/5.1	1.4 (0.6,2.8)	1.0 (-1.7,3.8)
Leukemia (excluding AML)	145,237	22/7.1	3.1 (1.9,4.7)	1.0 (0.4,1.7)	23/2.7	8.5 (5.4,12.7)	1.4 (0.7,2.0)	29/30.4	1.0 (0.6,1.4)	-0.1 (-0.8,0.6)
AML	13,029	11/0.7	16.6 (8.3,29.7)	7.9 (2.9,12.9)	3/0.2	12.6 (2.6,36.7)	2.1 (-0.5,4.7)	4/2.6	1.5 (0.4,3.9)	1.1 (-2.0,4.1)
Hodgkin Lymphoma	42,600	43/8.5	5.1 (3.7,6.8)	8.1 (5.1,11.1)	7/2.3	3.1 (1.2,6.4)	1.1 (-0.1,2.3)	15/14.8	1.0 (0.6,1.7)	0.0 (-1.7,1.8)
Non-Hodgkin Lymphoma	30,343	24/5.7	4.2 (2.7,6.2)	6.0 (2.9,9.2)	5/1.6	3.1 (1.0,7.4)	1.1 (-0.3,2.6)	11/9.6	1.1 (0.6,2.0)	0.4 (-1.7,2.6)
Neuroblastoma	28,500	8/2.5	3.3 (1.4,6.4)	1.9 (-0.0,3.9)	6/0.8	7.2 (2.6,15.7)	1.8 (0.1,3.5)	12/5.4	2.2 (1.1,3.9)	2.3 (-0.1,4.7)
Non-Heritable Retinoblastoma	26,167	2/4.1	0.5 (0.1,1.8)	-0.8 (-1.9,0.3)	1/1.3	0.8 (0.0,4.3)	-0.1 (-0.9,0.6)	4/5.9	0.7 (0.2,1.7)	-0.7 (-2.2,0.8)
Heritable Retinoblastoma	20,162	5/2.8	1.8 (0.6,4.2)	1.1 (-1.1,3.3)	4/0.9	4.5 (1.2,11.4)	1.5 (-0.4,3.5)	2/4.8	0.4 (0.1,1.5)	-1.4 (-2.7,0.0)
Wilms	51,519	27/4.7	5.8 (3.8,8.4)	4.3 (2.4,6.3)	7/1.6	4.4 (1.8,9.1)	1.1 (0.0,2.1)	16/11.4	1.4 (0.8,2.3)	0.9 (-0.6,2.4)
Bone Sarcoma	21,798	12/4.6	2.6 (1.4,4.6)	3.4 (0.3,6.5)	1/1.4	0.7 (0.0,4.1)	-0.2 (-1.1,0.7)	5/6.1	0.8 (0.3,1.9)	-0.5 (-2.5,1.5)
Soft Tissue Sarcoma	42,062	16/6.9	2.3 (1.3,3.8)	2.2 (0.3,4.0)	11/2.1	5.4 (2.7,9.6)	2.1 (0.6,3.7)	9/10.9	0.8 (0.4,1.6)	-0.5 (-1.9,0.9)
Other	55,891	27/8.2	3.3 (2.2,4.8)	3.4 (1.5,5.2)	9/2.7	3.3 (1.5,6.3)	1.1 (0.1,2.2)	10/12.7	0.8 (0.4,1.4)	-0.5 (-1.6,0.6)
*P*heterogeneity			<0.0001[a]	<0.0001[a]		<0.0001[a]	<0.0001[a]		0.0032[a]	0.0001[a]
Age at Diagnosis										
0-4 years	291,564	90/22.4	4.0 (3.2,4.9)	2.3 (1.7,3.0)	64/7.8	8.2 (6.3,10.4)	1.9 (1.4,2.5)	69/58.6	1.2 (0.9,1.5)	0.4 (-0.2,0.9)
5-9 years	163,195	84/19.2	4.4 (3.5,5.4)	4.0 (2.9,5.1)	43/6.0	7.2 (5.2,9.7)	2.3 (1.5,3.1)	46/43.1	1.1 (0.8,1.4)	0.2 (-0.6,1.0)
10-14 years	165,999	128/36.4	3.5 (2.9,4.2)	5.5 (4.2,6.9)	57/10.4	5.5 (4.1,7.1)	2.8 (1.9,3.7)	73/50.0	1.5 (1.1,1.8)	1.4 (0.4,2.4)
*P*heterogeneity			0.1296[a]	0.5264[a]		0.2464[a]	0.5622[a]		0.1579[a]	0.3301[a]
*P*trend			0.0432[a]	0.2835[a]		0.2618[a]	0.7383[a]		0.2578[a]	0.1478[a]

Table 5.3 (*continued*): Standardized mortality ratios and absolute excess risks for deaths due to all, neoplastic, non-neoplastic, circulatory, respiratory, and external causes, by potential explanatory factors

Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia, O: observed, E: expected, SMR: standardized mortality ratio, CI: confidence interval, AER: absolute excess risk

[a] *P*heterogeneity or *P*trend determined from multivariate Poisson model adjusting for sex, first primary neoplasm type, age at diagnosis, treatment era, and attained age

[b] *P*heterogeneity or *P*trend determined from multivariate Poisson model adjusting for sex, first primary neoplasm type, age at diagnosis, treatment era, and follow-up

		Circulatory Causes			Respiratory Causes			External Causes		
	Person-Years	**O/E**	**SMR (95%CI)**	**AER (95%CI)**	**O/E**	**SMR (95%CI)**	**AER (95%CI)**	**O/E**	**SMR (95%CI)**	**AER (95%CI)**
Treatment Era										
<1970	135,884	146/50.0	2.9 (2.5,3.4)	7.1 (5.3,8.8)	61/14.3	4.3 (3.3,5.5)	3.4 (2.3,4.6)	65/40.9	1.6 (1.2,2.0)	1.8 (0.6,2.9)
1970-1979	152,278	75/16.7	4.5 (3.5,5.6)	3.8 (2.7,4.9)	48/5.2	9.3 (6.8,12.3)	2.8 (1.9,3.7)	55/45.2	1.2 (0.9,1.6)	0.6 (-0.3,1.6)
1980-1989	155,375	63/7.8	8.1 (6.2,10.3)	3.6 (2.5,4.6)	36/2.9	12.4 (8.7,17.2)	2.1 (1.4,2.9)	41/38.9	1.1 (0.8,1.4)	0.1 (-0.7,0.9)
1990-2006	177,221	18/3.5	5.2 (3.1,8.2)	0.8 (0.4,1.3)	19/1.8	10.4 (6.2,16.2)	1.0 (0.5,1.5)	27/26.7	1.0 (0.7,1.5)	0.0 (-0.6,0.6)
*P*heterogeneity			0.0069[a]	0.0040[a]		0.1376[a]	0.0070[a]		0.3116[a]	0.0129[a]
*P*trend			0.2729[a]	0.1572[a]		0.2536[a]	0.0127[a]		0.0655[a]	0.0054[a]
Years Follow-Up										
5-19 years	390,711	70/9.7	7.2 (5.6,9.1)	1.5 (1.1,2.0)	69/6.4	10.8 (8.4,13.7)	1.6 (1.2,2.0)	99/82.4	1.2 (1.0,1.5)	0.4 (-0.1,0.9)
20-29 years	132,085	71/13.0	5.4 (4.3,6.9)	4.4 (3.1,5.6)	33/3.8	8.7 (6.0,12.2)	2.2 (1.4,3.1)	44/40.0	1.1 (0.8,1.5)	0.3 (-0.7,1.3)
30-39 years	66,379	68/20.9	3.3 (2.5,4.1)	7.1 (4.7,9.5)	32/4.4	7.2 (5.0,10.2)	4.2 (2.5,5.8)	29/20.2	1.4 (1.0,2.1)	1.3 (-0.3,2.9)
40-49 years	24,972	63/21.3	3.0 (2.3,3.8)	16.7 (10.5,22.9)	21/5.1	4.1 (2.5,6.3)	6.4 (2.8,10.0)	14/7.3	1.9 (1.0,3.2)	2.7 (-0.3,5.6)
50-59 years	6,102	27/11.2	2.4 (1.6,3.5)	25.9 (9.3,42.6)	8/3.7	2.1 (0.9,4.2)	7.0 (-2.1,16.1)	2/1.7	1.2 (0.1,4.3)	0.5 (-4.0,5.0)
60+ years	508	3/1.9	1.6 (0.3,4.6)	21.5 (-45.4,88.4)	1/0.8	1.2 (0.0,6.9)	3.9 (-34.7,42.5)	0/0.1	0.0 (0.0,0.0)	-3.0 (-3.0,-3.0)
*P*heterogeneity			0.0319[b]	<0.0001[b]		0.0509[b]	0.0062[b]		0.8808[b]	0.6821[b]
*P*trend			0.0011[b]	<0.0001[b]		0.0001[b]	0.0006[b]		0.8769[b]	0.1668[b]
Attained Age										
5-19 years	243,035	30/3.5	8.7 (5.8,12.4)	1.1 (0.7,1.5)	44/3.4	13.0 (9.4,17.4)	1.7 (1.1,2.2)	42/35.5	1.2 (0.9,1.6)	0.3 (-0.3,0.8)
20-29 years	195,584	56/7.6	7.3 (5.5,9.5)	2.5 (1.7,3.2)	35/3.7	9.3 (6.5,13.0)	1.6 (1.0,2.2)	69/61.4	1.1 (0.9,1.4)	0.4 (-0.4,1.2)
30-39 years	108,573	64/13.6	4.7 (3.6,6.0)	4.6 (3.2,6.1)	34/3.7	9.2 (6.4,12.8)	2.8 (1.7,3.8)	42/32.8	1.3 (0.9,1.7)	0.8 (-0.3,2.0)
40-49 years	51,869	69/21.8	3.2 (2.5,4.0)	9.1 (6.0,12.2)	27/4.3	6.3 (4.2,9.2)	4.4 (2.4,6.3)	23/15.9	1.4 (0.9,2.2)	1.4 (-0.4,3.2)
50-59 years	17,552	55/20.0	2.7 (2.1,3.6)	19.9 (11.7,28.2)	20/4.8	4.2 (2.5,6.4)	8.7 (3.7,13.7)	9/5.0	1.8 (0.8,3.4)	2.3 (-1.1,5.6)
60+ years	4,144	28/11.5	2.4 (1.6,3.5)	39.8 (14.8,64.8)	4/4.3	0.9 (0.3,2.4)	-0.8 (-10.3,8.6)	3/1.1	2.7 (0.6,8.0)	4.6 (-3.6,12.8)
*P*heterogeneity			0.0040[a]	<0.0001[a]		0.0002[a]	0.0139[a]		0.9779[a]	0.5122[a]
*P*trend			0.0002[a]	<0.0001[a]		0.0049[a]	0.0386[a]		0.7864[a]	0.0791[a]

Table 5.3 (*continued*): Standardized mortality ratios and absolute excess risks for deaths due to all, neoplastic, non-neoplastic, circulatory, respiratory, and external causes, by potential explanatory factors

Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia, O: observed, E: expected, SMR: standardized mortality ratio, CI: confidence interval, AER: absolute excess risk

[a] *P*heterogeneity or *P*trend determined from multivariate Poisson model adjusting for sex, first primary neoplasm type, age at diagnosis, treatment era, and attained age

[b] *P*heterogeneity or *P*trend determined from multivariate Poisson model adjusting for sex, first primary neoplasm type, age at diagnosis, treatment era, and follow-up

	All Causes			Neoplastic Causes			Non-Neoplastic Causes		
Treatment Era	**O/E**	**Univariate: EMR (95%CI)**	**Multivariate: EMR (95%CI)**	**O/E**	**Univariate: EMR (95%CI)**	**Multivariate: EMR (95%CI)**	**O/E**	**Univariate: EMR (95%CI)**	**Multivariate: EMR (95%CI)**
<1970	1333/228.1	1 (ref)	1 (ref)	936/79.7	1 (ref)	1 (ref)	397/148.5	1 (ref)	1 (ref)
1970-1979	1251/125.0	0.9 (0.8,1.0)	0.8 (0.7,0.8)	951/26.9	1.0 (0.9,1.1)	0.7 (0.7,0.8)	300/98.1	0.7 (0.6,0.9)	1.0 (0.8,1.3)
1980-1989	941/85.0	0.7 (0.6,0.7)	0.5 (0.4,0.6)	728/13.1	0.7 (0.7,0.8)	0.5 (0.4,0.5)	213/71.9	0.5 (0.4,0.6)	0.9 (0.6,1.1)
1990-2006	958/52.9	0.6 (0.6,0.7)	0.3 (0.3,0.4)	812/7.3	0.7 (0.6,0.8)	0.3 (0.3,0.4)	146/45.5	0.3 (0.2,0.4)	0.6 (0.4,0.8)
*P*trend		<0.0001	<0.0001		<0.0001	<0.0001		<0.0001	0.0016

Table 5.4: Excess mortality ratios from univariate and multivariate Poisson models assessing the risk of all causes, neoplastic causes, non-neoplastic causes, circulatory causes, respiratory, and external causes-of-death by treatment era

Multivariate Poisson model adjusted for sex, first primary neoplasm type, age at diagnosis, and attained age. *P*trend was calculated using likelihood ratio tests to assess the effect of treatment era

Abbreviations: O: observed, E: expected, EMR: excess mortality ratio, CI: confidence intervals

	Circulatory Causes			Respiratory Causes			External Causes		
Treatment Era	**O/E**	**Univariate: EMR (95%CI)**	**Multivariate: EMR (95%CI)**	**O/E**	**Univariate: EMR (95%CI)**	**Multivariate: EMR (95%CI)**	**O/E**	**Univariate: EMR (95%CI)**	**Multivariate: EMR (95%CI)**
<1970	146/50.0	1 (ref)	1 (ref)	61/14.3	1 (ref)	1 (ref)	65/40.9	1 (ref)	1 (ref)
1970-1979	75/16.7	0.5 (0.4,0.8)	0.9 (0.6,1.4)	48/5.2	0.8 (0.5,1.3)	1.0 (0.7,1.7)	55/45.2	0.4 (0.1,1.8)	0.7 (0.3,1.7)
1980-1989	63/7.8	0.5 (0.3,0.7)	1.2 (0.8,2.0)	36/2.9	0.6 (0.4,1.0)	0.9 (0.5,1.6)	41/38.9	0.1 (0.0,33.7)	0.5 (0.2,1.5)
1990-2006	18/3.5	0.1 (0.1,0.2)	0.4 (0.2,0.8)	19/1.8	0.3 (0.2,0.5)	0.4 (0.2,0.8)	27/26.7	0	0
*P*trend		<0.0001	0.1572		<0.0001	0.0127		0.0034	0.0054

Table 5.4 (*continued*): Excess mortality ratios from univariate and multivariate Poisson models assessing the risk of all causes, neoplastic causes, non-neoplastic causes, circulatory causes, respiratory, and external causes-of-death by treatment era

Multivariate Poisson model adjusted for sex, first primary neoplasm type, age at diagnosis, and attained age. *P*trend was calculated using likelihood ratio tests to assess the effect of treatment era

Abbreviations: O: observed, E: expected, EMR: excess mortality ratio, CI: confidence intervals

		All Causes					Neoplastic				Non-Neoplastic			
		Person-Years	O/E	SMR (95%CI)	AER (95%CI)	EMR (95%CI)	O/E	SMR (95%CI)	AER (95%CI)	EMR (95%CI)	O/E	SMR (95%CI)	AER (95%CI)	EMR (95%CI)
CNS (excluding PNET)	**<1970**	35,111	507/62.6	8.1 (7.4,8.8)	126.6 (114.0,139.1)	1.0 (ref)	328/22.6	14.5 (13.0,16.2)	87.0 (76.9,97.1)	1.0 (ref)	179/40.0	4.5 (3.8,5.2)	39.6 (32.1,47.1)	1.0 (ref)
	1970-1979	30,505	336/27.2	12.4 (11.1,13.8)	101.2 (89.5,113.0)	0.8 (0.7,0.9)	235/6.2	37.7 (33.1,42.9)	75.0 (65.1,84.8)	0.8 (0.6,0.9)	101/20.9	4.8 (3.9,5.9)	26.2 (19.8,32.7)	1.0 (0.7,1.4)
	1980-1989	24,887	252/15.0	16.8 (14.8,19.0)	95.2 (82.7,107.7)	0.7 (0.6,0.8)	192/2.4	80.4 (69.4,92.6)	76.2 (65.3,87.1)	0.7 (0.6,0.8)	60/12.6	4.8 (3.6,6.1)	19.0 (12.9,25.1)	0.9 (0.6,1.3)
	1990-2006	34,248	241/10.8	22.3 (19.6,25.3)	67.2 (58.3,76.1)	0.4 (0.3,0.5)	202/1.5	136.6 (118.4,156.8)	58.6 (50.4,66.7)	0.4 (0.3,0.5)	39/9.3	4.2 (3.0,5.7)	8.7 (5.1,12.2)	0.5 (0.3,0.9)
	*P*trend			0.0372	<0.0001[a]	<0.0001		0.0614[b]	<0.0001[a]	<0.0001[b]		0.8823[b]	<0.0001[a]	0.0229[b]
CNS PNET	**<1970**	4,487	106/6.6	16.0 (13.1,19.3)	221.4 (176.5,266.4)	1.0 (ref)	88/2.1	42.9 (34.4,52.9)	191.6 (150.6,232.5)	1.0 (ref)	18/4.6	3.9 (2.3,6.2)	29.9 (11.4,48.4)	1.0 (ref)
	1970-1979	4,160	76/3.5	21.9 (17.2,27.4)	174.3 (133.3,215.4)	0.7 (0.5,1.0)	57/0.7	84.0 (63.6,108.8)	135.4 (99.8,171.0)	0.6 (0.4,0.9)	19/2.8	6.8 (4.1,10.6)	39.0 (18.4,59.5)	1.9 (0.7,4.8)
	1980-1989	4,510	67/2.7	24.9 (19.3,31.7)	142.6 (107.0,178.2)	0.6 (0.4,0.8)	58/0.4	155.0 (117.7,200.4)	127.8 (94.7,160.9)	0.5 (0.4,0.8)	9/2.3	3.9 (1.8,7.4)	14.8 (1.8,27.9)	1.2 (0.4,4.0)
	1990-2006	5,542	92/1.8	50.9 (41.0,62.4)	162.7 (128.8,196.7)	0.5 (0.3,0.6)	85/0.2	361.5 (288.8,447.0)	152.9 (120.3,185.5)	0.4 (0.3,0.6)	7/1.6	4.5 (1.8,9.2)	9.8 (0.4,19.1)	0.8 (0.2,2.8)
	*P*trend			0.4530[b]	0.0246[a]	<0.0001[b]		0.5124[b]	0.1526[a]	<0.0001[b]		0.7999[b]	0.0434[a]	0.6843[b]
Leukemia (excluding AML)	**<1970**	3,256	98/4.1	24.0 (19.5,29.3)	288.4 (228.8,348.0)	1.0 (ref)	95/1.3	75.2 (60.8,91.9)	287.9 (229.2,346.5)	1.0 (ref)	3/2.8	1.1 (0.2,3.1)	0.6 (-9.9,11.0)	1.0 (ref)
	1970-1979	40,452	414/29.2	14.2 (12.8,15.6)	95.1 (85.3,105.0)	0.3 (0.2,0.4)	359/5.9	60.6 (54.5,67.2)	87.3 (78.1,96.5)	0.3 (0.2,0.3)	55/23.3	2.4 (1.8,3.1)	7.8 (4.2,11.4)	*NA*
	1980-1989	47,088	288/23.1	12.5 (11.1,14.0)	56.3 (49.2,63.3)	0.1 (0.1,0.2)	238/3.4	69.3 (60.7,78.6)	49.8 (43.4,56.2)	0.1 (0.1,0.2)	50/19.6	2.5 (1.9,3.4)	6.5 (3.5,9.4)	*NA*
	1990-2006	54,441	303/14.8	20.4 (18.2,22.9)	52.9 (46.7,59.2)	0.1 (0.1,0.1)	263/2.1	125.8 (111.0,142.0)	47.9 (42.1,53.8)	0.1 (0.1,0.1)	40/12.7	3.1 (2.2,4.3)	5.0 (2.7,7.3)	*NA*
	*P*trend			<0.0001[b]	<0.0001[a]	<0.0001[b]		<0.0001[b]	<0.0001[a]	<0.0001[b]		0.9337[b]	0.3789[a]	0.0962[b]
AML	**<1970**	409	2/0.6	3.3 (0.4,11.9)	34.1 (-33.8,101.9)	1.0 (ref)	2/0.2	11.4 (1.4,41.1)	44.7 (-23.2,112.5)	1.0 (ref)	0/0.4	0	-10.6 (-10.6,-10.6)	1.0 (ref)
	1970-1979	1,878	14/1.6	8.5 (4.7,14.3)	65.8 (26.8,104.9)	1.8 (0.3,10.5)	11/0.3	32.3 (16.1,57.8)	56.8 (22.2,91.4)	0.9 (0.2,5.0)	3/1.3	2.3 (0.5,6.7)	9.0 (-9.0,27.1)	*NA*
	1980-1989	3,976	36/2.0	18.1 (12.7,25.1)	85.6 (56.0,115.1)	2.3 (0.4,13.5)	22/0.3	70.7 (44.3,107.0)	54.6 (31.4,77.7)	0.8 (0.2,4.3)	14/1.7	8.4 (4.6,14.0)	31.0 (12.6,49.4)	*NA*
	1990-2006	6,768	30/2.0	15.2 (10.3,21.7)	41.4 (25.6,57.3)	0.9 (0.1,5.3)	21/0.3	75.9 (47.0,116.0)	30.6 (17.3,43.9)	0.3 (0.1,1.7)	9/1.7	5.3 (2.4,10.1)	10.8 (2.1,19.5)	*NA*
	*P*trend			0.8310[b]	0.1324[a]	0.0279[b]		0.1171[b]	0.0914[a]	0.0035[b]		0.0225[b]	0.9294[a]	0.2389[b]
Hodgkin Lymphoma	**<1970**	8,690	157/19.2	8.2 (6.9,9.6)	158.5 (130.3,186.8)	1.0 (ref)	121/6.5	18.7 (15.5,22.4)	131.8 (107.0,156.6)	1.0 (ref)	36/12.8	2.8 (2.0,3.9)	26.7 (13.2,40.3)	1.0 (ref)
	1970-1979	13,011	108/14.8	7.3 (6.0,8.8)	71.7 (56.0,87.3)	0.4 (0.3,0.6)	74/3.2	23.4 (18.4,29.4)	54.4 (41.5,67.4)	0.4 (0.3,0.5)	34/11.6	2.9 (2.0,4.1)	17.2 (8.4,26.0)	0.8 (0.3,1.8)
	1980-1989	11,424	42/9.1	4.6 (3.3,6.2)	28.8 (17.7,39.9)	0.2 (0.1,0.2)	29/1.4	20.6 (13.8,29.6)	24.2 (14.9,33.4)	0.1 (0.1,0.2)	13/7.7	1.7 (0.9,2.9)	4.6 (-1.6,10.8)	0.4 (0.1,1.1)
	1990-2006	9,475	28/4.2	6.6 (4.4,9.6)	25.1 (14.1,36.0)	0.1 (0.1,0.1)	19/0.5	37.1 (22.3,57.9)	19.5 (10.5,28.5)	0.1 (0.0,0.1)	9/3.7	2.4 (1.1,4.6)	5.6 (-0.6,11.8)	0.3 (0.1,1.1)
	*P*trend			<0.0001[b]	<0.0001[a]	<0.0001[b]		<0.0001[b]	<0.0001[a]	<0.0001[b]		0.1327[b]	0.0023[a]	0.0237[b]

Table 5.5: Standardized mortality ratios, absolute excess risks, and excess mortality ratios for all, neoplastic, and non-neoplastic causes-of-death, by first primary neoplastic type and treatment era

Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia, O: observed, E: expected, SMR: standardized mortality ratio, CI: confidence interval, AER: absolute excess risk, EMR: excess mortality ratio, NA: not possible to reliably calculate due to very small numbers

[a] *P*trend determined from univariate Poisson model

[b] *P*trend determined from multivariate Poisson model adjusting for sex, first primary neoplasm type, age at diagnosis, treatment era, and attained age

		All Causes					Neoplastic				Non-Neoplastic			
		Person-Years	O/E	SMR (95%CI)	AER (95%CI)	EMR (95%CI)	O/E	SMR (95%CI)	AER (95%CI)	EMR (95%CI)	O/E	SMR (95%CI)	AER (95%CI)	EMR (95%CI)
Non-Hodgkin Lymphoma	**<1970**	7,071	46/15.7	2.9 (2.1,3.9)	42.8 (24.0,61.6)	1.0 (ref)	24/5.6	4.3 (2.8,6.4)	26.1 (12.5,39.6)	1.0 (ref)	22/10.2	2.2 (1.4,3.3)	16.7 (3.7,29.7)	1.0 (ref)
	1970-1979	6,264	27/6.5	4.2 (2.7,6.1)	32.8 (16.5,49.0)	0.9 (0.5,1.7)	20/1.3	15.0 (9.2,23.2)	29.8 (15.8,43.8)	1.3 (0.6,2.7)	7/5.2	1.4 (0.5,2.8)	2.9 (-5.3,11.2)	0.5 (0.1,2.2)
	1980-1989	9,047	31/6.3	4.9 (3.3,6.9)	27.3 (15.2,39.3)	0.6 (0.3,1.2)	16/0.9	18.2 (10.4,29.5)	16.7 (8.0,25.4)	0.6 (0.3,1.3)	15/5.5	2.7 (1.5,4.5)	10.5 (2.2,18.9)	0.7 (0.2,3.0)
	1990-2006	7,962	27/3.3	8.1 (5.3,11.8)	29.7 (16.9,42.5)	0.5 (0.3,1.0)	19/0.4	47.5 (28.6,74.2)	23.4 (12.6,34.1)	0.6 (0.3,1.2)	8/2.9	2.7 (1.2,5.4)	6.4 (-0.6,13.3)	0.3 (0.0,2.7)
	*P*trend			0.9035[b]	0.2571[a]	0.0257[b]		0.9692[b]	0.4696[a]	0.0411[b]		0.9388[b]	0.3995[a]	0.3268[b]
Neuroblastoma	**<1970**	8,798	49/10.1	4.8 (3.6,6.4)	44.2 (28.6,59.8)	1.0 (ref)	29/3.1	9.4 (6.3,13.6)	29.5 (17.5,41.5)	1.0 (ref)	20/7.1	2.8 (1.7,4.4)	14.7 (4.7,24.7)	1.0 (ref)
	1970-1979	4,584	23/2.7	8.4 (5.3,12.6)	44.2 (23.7,64.7)	1.1 (0.6,1.9)	18/0.5	38.5 (22.8,60.8)	38.2 (20.1,56.4)	1.2 (0.6,2.2)	5/2.3	2.2 (0.7,5.2)	6.0 (-3.6,15.5)	0.8 (0.2,3.0)
	1980-1989	6,739	29/2.5	11.6 (7.8,16.7)	39.3 (23.7,55.0)	0.8 (0.5,1.5)	21/0.4	58.9 (36.5,90.0)	30.6 (17.3,44.0)	0.8 (0.4,1.5)	8/2.1	3.7 (1.6,7.4)	8.7 (0.5,16.9)	0.7 (0.2,2.8)
	1990-2006	8,380	43/1.5	28.9 (20.9,38.9)	49.5 (34.2,64.9)	0.8 (0.5,1.4)	39/0.3	150.6 (107.1,205.8)	46.2 (31.6,60.8)	0.9 (0.5,1.6)	4/1.2	3.3 (0.9,8.3)	3.3 (-1.4,8.0)	0.3 (0.1,2.1)
	*P*trend			0.0212[b]	0.7274[a]	0.3290[b]		0.0271[b]	0.5834[a]	0.4944		0.9201	0.0596[a]	0.2502[b]
Non-Heritable Retinoblastoma	**<1970**	11,822	19/17.0	1.1 (0.7,1.8)	1.7 (-5.5,9.0)	1.0 (ref)	13/5.8	2.2 (1.2,3.8)	6.1 (0.1,12.1)	1.0 (ref)	6/11.2	0.5 (0.2,1.2)	-4.4 (-8.4,-0.3)	1.0 (ref)
	1970-1979	6,498	9/4.1	2.2 (1.0,4.2)	7.6 (-1.5,16.6)	9.0 (0.1,1357.2)	1/0.7	1.4 (0.0,7.7)	0.4 (-2.6,3.4)	0.4 (0.0,8.2)	8/3.4	2.4 (1.0,4.7)	7.1 (-1.4,15.7)	*NA*
	1980-1989	3,720	2/1.4	1.4 (0.2,5.2)	1.6 (-5.8,9.1)	13.2 (0.0,6321.2)	1/0.2	5.1 (0.1,28.3)	2.2 (-3.1,7.4)	2.0 (0.1,50.7)	1/1.2	0.8 (0.0,4.7)	-0.5 (-5.8,4.8)	*NA*
	1990-2006	4,127	1/0.8	1.3 (0.0,7.3)	0.6 (-4.2,5.3)	*NA*	0/0.1	0	-0.3 (-0.3,-0.3)	*NA*	1/0.6	1.6 (0.0,8.8)	0.9 (-3.9,5.6)	*NA*
	*P*trend			0.5205[b]	0.9396[a]	0.9222[b]		0.6345[b]	0.1790[a]	0.6214[b]		0.2701[b]	0.5799[a]	0.7566[b]
Heritable Retinoblastoma	**<1970**	10,939	97/13.2	7.3 (5.9,8.9)	76.6 (58.9,94.2)	1.0 (ref)	83/4.1	20.1 (16.0,25.0)	72.1 (55.8,88.4)	1.0 (ref)	14/9.1	1.5 (0.8,2.6)	4.5 (-2.2,11.2)	1.0 (ref)
	1970-1979	3,996	21/2.3	9.2 (5.7,14.1)	46.8 (24.4,69.3)	0.8 (0.5,1.5)	18/0.4	46.9 (27.8,74.1)	44.1 (23.3,64.9)	0.8 (0.5,1.5)	3/1.9	1.6 (0.3,4.6)	2.8 (-5.7,11.3)	*NA*
	1980-1989	2,835	17/1.0	17.0 (9.9,27.3)	56.4 (27.9,84.9)	1.0 (0.6,1.9)	16/0.1	112.9 (64.5,183.4)	55.9 (28.3,83.6)	1.1 (0.6,1.9)	1/0.9	1.2 (0.0,6.5)	0.5 (-6.4,7.4)	2.5 (0.1,61.7)
	1990-2006	2,392	4/0.4	9.9 (2.7,25.4)	15.0 (-1.4,31.4)	0.2 (0.1,0.8)	4/0.1	54.8 (14.9,140.3)	16.4 (0.0,32.8)	0.3 (0.1,0.8)	0/0.3	0	-1.4 (-1.4,-1.4)	*NA*
	*P*trend			0.6699[b]	0.0011[a]	0.0399[b]		0.6289[b]	0.0019[a]	0.0594[b]		0.6380[b]	0.2283[a]	1.0000[b]
Wilms	**<1970**	13,514	75/16.6	4.5 (3.6,5.7)	43.2 (30.7,55.8)	1.0 (ref)	40/5.2	7.7 (5.5,10.5)	25.7 (16.6,34.9)	1.0 (ref)	35/11.4	3. 1 (2.1,4.3)	17.5 (8.9,26.1)	1.0 (ref)
	1970-1979	15,121	65/10.0	6.5 (5.0,8.3)	36.3 (25.9,46.8)	1.2 (0.8,1.9)	36/1.8	19.8 (13.9,27.4)	22.6 (14.8,30.4)	1.0 (0.6,1.7)	29/8.2	3.5 (2.4,5.1)	13.7 (6.8,20.7)	1.6 (0.7,3.5)
	1980-1989	11,964	29/4.9	5.9 (3.9,8.4)	20.1 (11.3,28.9)	0.8 (0.4,1.4)	13/0.7	18.2 (9.7,31.1)	10.3 (4.4,16.2)	0.5 (0.2,1.0)	16/4.2	3.8 (2.2,6.2)	9.8 (3.3,16.4)	2.0 (0.7,5.5)
	1990-2006	10,920	15/2.3	6.6 (3.7,10.8)	11.6 (4.7,18.6)	0.5 (0.2,1.0)	12/0.4	32.9 (17.0,57.5)	10.7 (4.4,16.9)	0.4 (0.2,0.9)	3/1.9	1.6 (0.3,4.6)	1.0 (-2.1,4.1)	*NA*
	*P*trend			0.8409[b]	<0.0001[a]	0.0509[b]		0.5596[b]	0.0020[a]	0.0070[b]		0.2889[b]	0.0117[a]	0.6925[b]

Table 5.5 (*continued*): Standardized mortality ratios, absolute excess risks, and excess mortality ratios for all, neoplastic, and non-neoplastic causes-of-death, by first primary neoplastic type and treatment era

Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia, O: observed, E: expected, SMR: standardized mortality ratio, CI: confidence interval, AER: absolute excess risk, EMR: excess mortality ratio, NA: not possible to reliably calculate due to very small numbers

[a] *P*trend determined from univariate Poisson model

[b] *P*trend determined from multivariate Poisson model adjusting for sex, first primary neoplasm type, age at diagnosis, treatment era, and attained age

			All Causes				Neoplastic				Non-Neoplastic			
		Person Years	O/E	SMR (95%CI)	AER (95%CI)	EMR (95%CI)	O/E	SMR (95%CI)	AER (95%CI)	EMR (95%CI)	O/E	SMR (95%CI)	AER (95%CI)	EMR (95%CI)
Bone Sarcoma	**<1970**	5,634	48/13.2	3.6 (2.7,4.8)	61.9 (37.8,86.0)	1.0 (ref)	38/5.2	7.4 (5.2,10.1)	58.3 (36.8,79.7)	1.0 (ref)	10/8.0	1.3 (0.6,2.3)	3.6 (-7.4,14.6)	1.0 (ref)
	1970-1979	5,004	41/5.3	7.8 (5.6,10.5)	71.4 (46.3,96.4)	0.9 (0.5,1.4)	33/1.3	25.0 (17.2,35.1)	63.3 (40.8,85.8)	0.8 (0.5,1.4)	8/4.0	2.0 (0.9,4.0)	8.1 (-3.0,19.1)	0.2 (0.0,1349.8)
	1980-1989	5,635	44/3.9	11.3 (8.2,15.1)	71.2 (48.1,94.2)	0.8 (0.5,1.3)	40/0.7	60.4 (43.2,82.3)	69.8 (47.8,91.8)	0.8 (0.5,1.3)	4/3.2	1.2 (0.3,3.2)	1.4 (-5.6,8.3)	*NA*
	1990-2006	5,524	65/2.3	28.5 (22.0,36.3)	113.5 (84.9,142.1)	0.8 (0.5,1.2)	61/0.3	207.9 (159.0,267.1)	109.9 (82.2,137.6)	0.8 (0.5,1.3)	4/2.0	2.0 (0.5,5.2)	3.6 (-3.5,10.7)	1.1 (0.1,9.6)
	*P*trend			0.0728[b]	0.0110[a]	0.3485[b]		0.0187[b]	0.0046[a]	0.3815[b]		0.8644[b]	0.6998[a]	0.7485[b]
Soft Tissue Sarcoma	**<1970**	12,458	60/22.9	2.6 (2.0,3.4)	29.8 (17.6,42.0)	1.0 (ref)	39/8.0	4.8 (3.4,6.6)	24.9 (15.0,34.7)	1.0 (ref)	21/14.8	1.4 (0.9,2.2)	5.0 (-2.3,12.2)	1.0 (ref)
	1970-1979	8,739	66/7.3	9.0 (7.0,11.4)	67.1 (48.9,85.3)	1.7 (1.1,2.7)	51/1.5	33.2 (24.7,43.6)	56.6 (40.6,72.6)	1.8 (1.1,2.8)	15/5.8	2.6 (1.4,4.3)	10.5 (1.8,19.2)	3.0 (0.4,24.0)
	1980-1989	9,975	53/5.6	9.5 (7.1,12.4)	47.5 (33.2,61.8)	1.1 (0.7,1.7)	44/0.9	51.5 (37.4,69.1)	43.3 (30.2,56.3)	1.1 (0.7,1.9)	9/4.7	1.9 (0.9,3.6)	4.3 (-1.6,10.2)	0.8 (0.1,10.5)
	1990-2006	10,891	74/3.4	21.6 (16.9,27.1)	64.8 (49.3,80.3)	1.1 (0.7,1.7)	65/0.5	138.9 (107.2,177.0)	59.3 (44.7,73.8)	1.1 (0.7,1.8)	9/3.0	3.0 (1.4,5.8)	5.5 (0.1,10.9)	2.2 (0.3,19.6)
	*P*trend			0.0032[b]	0.0140[a]	0.4951[b]		0.0021[b]	0.0023[a]	0.5906[b]		0.6827[b]	0.9485[a]	0.6588[b]
Other	**<1970**	13,695	69/26.3	2.6 (2.0,3.3)	31.2 (19.3,43.0)	1.0 (ref)	36/10.1	3.5 (2.5,4.9)	18.9 (10.3,27.5)	1.0 (ref)	33/16.2	2.0 (1.4,2.9)	12.3 (4.1,20.5)	1.0 (ref)
	1970-1979	12,067	51/10.5	4.9 (3.6,6.4)	33.6 (22.0,45.2)	0.9 (0.5,1.4)	38/2.9	13.0 (9.2,17.8)	29.1 (19.0,39.1)	1.1 (0.6,1.8)	13/7.5	1.7 (0.9,3.0)	4.5 (-1.3,10.4)	0.4 (0.1,1.7)
	1980-1989	13,576	51/7.5	6.8 (5.1,9.0)	32.1 (21.7,42.4)	0.8 (0.5,1.2)	38/1.4	28.0 (19.8,38.5)	27.0 (18.1,35.9)	0.9 (0.5,1.5)	13/6.1	2.1 (1.1,3.6)	5.1 (-0.1,10.3)	0.4 (0.1,1.7)
	1990-2006	16,552	35/5.3	6.6 (4.6,9.2)	18.0 (11.0,25.0)	0.3 (0.2,0.6)	22/0.7	29.4 (18.4,44.4)	12.8 (7.3,18.4)	0.3 (0.2,0.6)	13/4.5	2.9 (1.5,4.9)	5.1 (0.9,9.4)	0.6 (0.2,2.2)
	*P*trend			0.2055[b]	0.0095[a]	0.0001[b]		0.3501[b]	0.0520[a]	0.0001[b]		0.7290[b]	0.0947[a]	0.4198[b]

Table 5.5 (*continued*): Standardized mortality ratios, absolute excess risks, and excess mortality ratios for all, neoplastic, and non-neoplastic causes-of-death, by first primary neoplastic type and treatment era

Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia, O: observed, E: expected, SMR: standardized mortality ratio, CI: confidence interval, AER: absolute excess risk, EMR: excess mortality ratio, NA: not possible to reliably calculate due to very small numbers

[a]*P*trend determined from univariate Poisson model

[b]*P*trend determined from multivariate Poisson model adjusting for sex, first primary neoplasm type, age at diagnosis, treatment era, and attained age

	Attained Age																	
	5-19 years			20-29 years			30-39 years			40-49 years			50-59 years			60+ years		
	O/E	AER	% Total	O/E	AER	% Total	O/E	AER	% Total	O/E	AER	% Total	O/E	AER	% Total	O/E	AER	% Total
Neoplastic	2022/ 10.1	82.8	92.3	739/ 13.7	37.1	81.2	324/ 20.2	28	69.0	184/ 30.5	29.6	56.7	117/ 32.5	48.2	52.3	41/ 19.9	50.8	47.0
Non-Neoplastic	228/ 60.4	6.9	7.7	266/ 97.5	8.6	18.8	212/ 74.6	12.7	31.3	182/ 64.6	22.6	43.3	121/ 43.6	44.1	47.8	47/ 23.3	57.3	53.0
Circulatory	30/ 3.5	1.1	1.2	56/ 7.6	2.5	5.5	64/ 13.6	4.6	11.3	69/ 21.8	9.1	17.4	55/ 20.0	19.9	21.6	28/ 11.5	39.8	36.8
Respiratory	44/ 3.4	1.7	1.9	35/ 3.7	1.6	3.5	34/ 3.7	2.8	6.9	27/ 4.3	4.4	8.4	20/ 4.8	8.7	9.4	4/ 4.3	-0.8	-0.7
External	42/ 35.5	0.3	0.3	69/ 61.4	0.4	0.9	42/ 32.8	0.8	2.0	23/ 15.9	1.4	2.7	9/ 5.0	2.3	2.5	3/ 1.1	4.6	4.3
Other Non-Neoplastic[a]	112/ 18.0	3.9	4.4	106/ 24.7	4.2	9.2	72/ 24.5	4.4	10.8	63/ 22.6	7.8	14.9	37/ 13.8	13.2	14.3	12/ 6.3	13.7	12.7
All Causes	2250/ 70.5	89.7	100.0	1005/ 111.2	45.7	100.0	536/ 94.8	40.6	100.0	366/ 95.1	52.2	100.0	238/ 76.1	92.2	100.0	88/ 43.2	108.1	100.0

Table 5.6: Absolute excess risks (AER) for neoplastic, non-neoplastic, circulatory, respiratory, external and other non-neoplastic[a] causes-of-death by attained age as a proportion of total excess risk

[a]Includes the following causes-of-death: nervous, infection, digestive, perinatal, endocrine, genitourinary, musculoskeletal, mental, blood, other

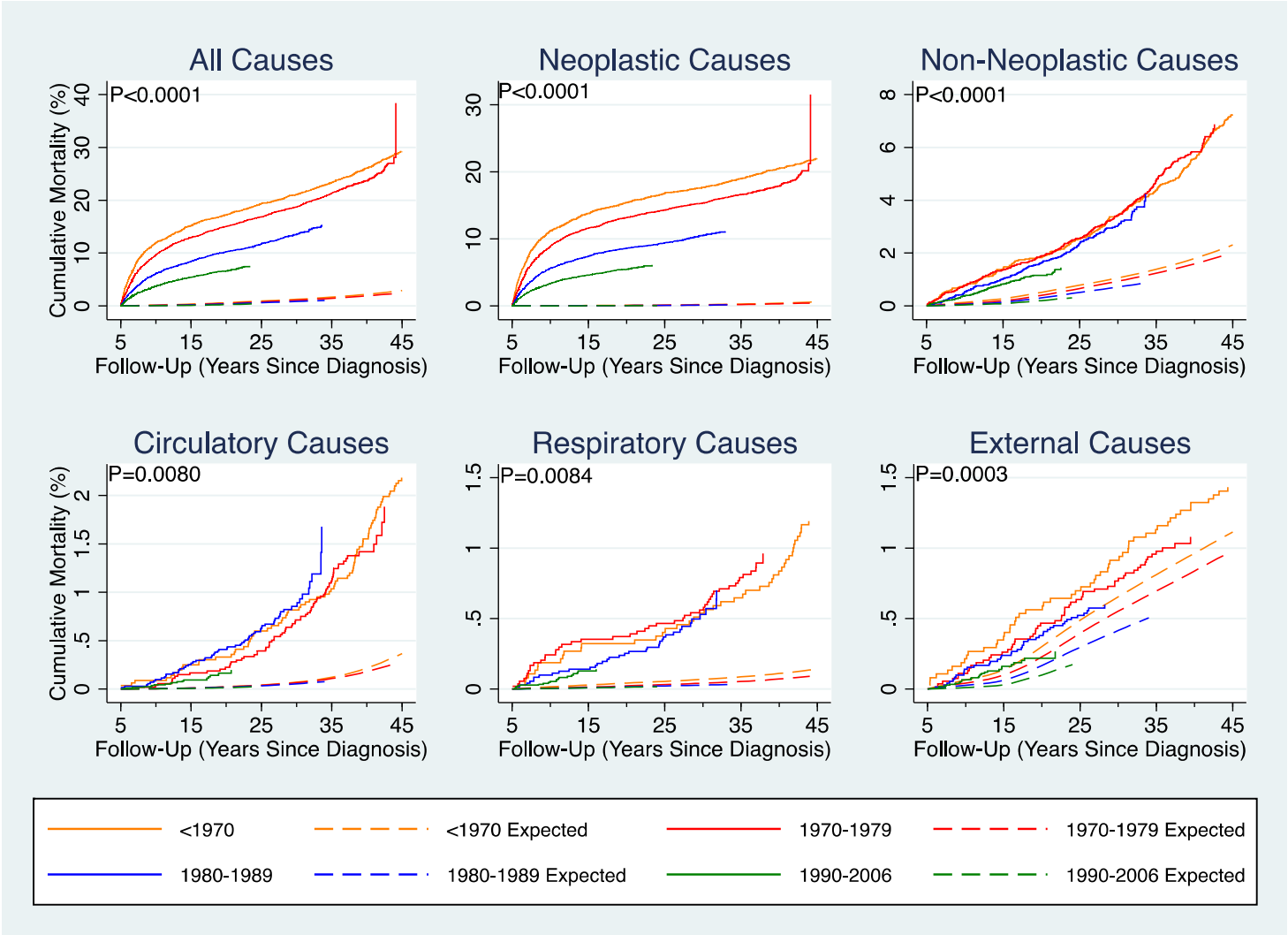

Figure 5.1: Observed (among survivors) and expected cumulative mortalities for all, neoplastic, non-neoplastic, circulatory, respiratory, and external causes-of-death, by follow-up (years since diagnosis), stratified by treatment era

P determined using a log-rank test

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CHAPTER 6

STUDY 4:

Population-based long-term cardiac-specific mortality among 34,489 five-year survivors of childhood cancer in Great Britain

Abstract

Purpose: Increased risks of cardiac morbidity and mortality among childhood cancer survivors have been described previously. However, little is known about the long-term risks of cardiac mortality and whether the risk has decreased among those more recently diagnosed. We investigated the risk of long-term cardiac mortality among survivors within the recently extended British Childhood Cancer Survivor Study (BCCSS).

Material and Methods: The BCCSS is a population-based cohort of 34,489 five-year survivors of childhood cancer diagnosed from 1940-2006, and is the largest cohort to date to assess late mortality. Standardized mortality ratios (SMRs) and absolute excess risks (AERs) were used to quantify cardiac mortality excess risk.

Results: Overall, 182 cardiac deaths were observed, which was 3.4-times the number expected. By cardiac subgroups, survivors were 2.5-times and 5.9-times more at risk of ischemic heart disease (IHD) and cardiomyopathy/heart failure (CM/HF) death than expected, respectively. Although the SMR declined with age, 13 excess cardiac deaths per 10,000 person-years were observed beyond age 50. When treatment era was assessed, a quadratic relationship was identified for overall cardiac and CM/HF deaths, where the excess risk was greatest among those diagnosed from 1980-1989. Specifically for CM/HF deaths, survivors diagnosed from 1980-1989 had 28.9-times more excess deaths than survivors diagnosed either before 1970 or after 1990, after adjustment.

Conclusions: Excess cardiac mortality among five-year survivors of childhood cancer remains increased beyond 50 years age. However, the fact that the risk was greatest in those diagnosed from 1980-1989 suggests that initiatives to reduce cardiac toxicity among those treated more recently may be having a measurable impact.

Introduction

Survival from childhood cancer has improved substantially over recent decades, with approximately 80% of those diagnosed now surviving at least five years[1]. Consequently, as survival prospects continue to increase, the number of survivors will also rise. Currently, there are an estimated 33,000 survivors of childhood cancer in the U.K.[2], and approximately 300,000-500,000 survivors in Europe[3]. With the population of survivors of childhood cancer growing, it becomes ever more important to assess outcomes post five-year survival as curative treatments are associated with long-term adverse effects, ultimately increasing the risk of premature mortality.

Radiation and chemotherapy increase the risk of cardiovascular disease in survivors of childhood cancer[4,5]. Previous reports have shown that cardiovascular death accounts for a large proportion of the excess mortality and for some types of childhood cancer is the leading cause of non-neoplastic mortality[6,7]. However, most previous studies have been restricted due to limited follow-up and small numbers of cardiac deaths, and thus have not been able to satisfactorily address the risk of cardiac mortality beyond 50 years age nor determine whether long-term excess mortality has declined for survivors treated in more recent treatment eras. Thus, we investigated the long-term risk of cardiac mortality among nearly 35,000 survivors of childhood cancer diagnosed from 0-14 years within the British Childhood Cancer Survivor Study (BCCSS). The BCCSS is the largest study to date to assess long-term mortality in survivors of childhood cancer. Furthermore, key advantages of the BCCSS compared to other studies are that it is a large, population-based cohort that spans from the 1940s to 2000s, making it possible to assess short- and long-term cardiac mortality as well as changes in mortality in relation to treatment era.

Material and Methods

British Childhood Cancer Survivor Study

The BCCSS comprises 34,489 five-year survivors of childhood cancer diagnosed from 1940-2006 under the age of 15 years in Britain. The cohort was identified using the National Registry of Childhood Tumors, which has a high estimated level of ascertainment (~99%)[8]. Ethical approval for the study was obtained from the National Research Ethics Service and legal approval to process identifiable data without consent was approved by the Confidentiality Advisory Group.

We developed a proxy for chest irradiation and anthracycline exposure based upon first primary neoplasm (FPN) type and year of diagnosis using the following categories: (i) unlikely exposed to either chest irradiation or anthracyclines, (ii) likely exposed to chest irradiation, but unlikely exposed to anthracyclines – henceforth called 'likely exposed to chest irradiation,' (iii) likely exposed to anthracyclines, but unlikely exposed to chest irradiation – henceforth called 'likely exposed to anthracyclines,' and (iv) likely exposed to both chest irradiation and anthracyclines (**Table 6.1**). Survivors diagnosed before 1975 with Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), neuroblastoma, Wilms, and bone sarcoma were categorized as being likely exposed to chest irradiation. Survivors diagnosed between 1975-2006 with leukemia, Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL), neuroblastoma, Wilms, bone sarcoma, or soft-tissue sarcoma were categorized as being likely exposed to anthracyclines. Survivors of HL, NHL, neuroblastoma, and Wilms were also likely to be exposed to chest irradiation if diagnosed from 1975 onwards. All survivors of primitive neuroectodermal tumors (PNET) of the central nervous system (CNS) were categorized as being likely exposed to chest irradiation.

Death Ascertainment

By linking with the Health and Social Care Information Centre, the BCCSS cohort was able to ascertain each survivor's vital and embarkation status. For each death, an attempt was made to obtain the death certificate and underlying cause-of-death as coded by the Office of National Statistics (England and Wales) and General Registrar Office (Scotland) using the relevant *International Classification of Diseases* (ICD). ICD codes corresponding to a cardiac death were identified and sub-categorized into clinically relevant groups for analysis, specifically: ischemic heart disease (IHD), cardiomyopathy/heart failure (CM/HF), arrhythmias, pericardial disease, and valvular disease (**Table 6.2**). Follow-up for cardiac mortality commenced at five-year survival and continued until the first instance of emigration, death, or February 28, 2014.

Statistical Analyses

Standardized mortality ratios (SMRs) and absolute excess risks (AERs) were calculated using standard cohort techniques[9]. The SMR was defined as the ratio of the observed over expected number of deaths. The AER was defined as the observed minus the expected number of deaths divided by person-years at risk multiplied by 10,000. Expected numbers were calculated by multiplying the person-years for each sex-specific, age-specific (quinquennial), and calendar year-specific (single year) stratum by the corresponding mortality rate for the population of England and Wales and then summing across the strata[10]. Multivariable Poisson regression models for the SMRs and AERs were used to evaluate the simultaneous effect of the following demographic- and cancer-related factors: sex, FPN type, age at cancer diagnosis, treatment era, and attained age. If the results from the univariate and multivariate models were similar (implying little confounding), then the univariate findings were reported in terms of SMRs and

AERs. If the results from the models differed (implying confounding), then the multivariate results were reported in terms of relative risks for the SMRs and excess mortality ratios for the AERs. To test for heterogeneity, trend, or nonlinear relationships, likelihood-ratio tests within Poisson regression models were used.

Cumulative mortality, as a function of follow-up (years since five-year survival), was estimated by using the stcompet command in Stata[11]. Causes-of-death other than the one under study were treated as competing risks[12].

All analyses were completed using Stata statistical software[11], where the criterion for statistical significance was a two-sided *P*-value less than 0.05.

Results

Study Characteristics

From five-year survival, the cohort was followed up for a total of 620,758 person-years, with a mean follow-up of 18.0 (range:0.0-68.7) years and to a mean attained age of 29.6 (range:5.5-85.6) years at end of follow-up. By the study exit date, 4,483 (13%) individuals in the cohort had died, of which 182 (4.1%) were attributed to cardiac causes (**Table 6.3**). From five-year survival, the mean follow-up time and attained age to cardiac death was 26.4 and 39.2 years, respectively, which was higher than that observed for individuals who died from a non-cardiac cause. Males accounted for approximately two-thirds (63.7%) of the cardiac deaths, and survivors of CNS tumors (excluding PNET), HL, and Wilms accounted for nearly 50% of the cardiac deaths observed when combined.

Overall Cardiac Mortality

Survivors of childhood cancer experienced 3.4-times (95%CI:2.9-4.0) the number of cardiac deaths expected from the general population, which equated to 2.1 (95%CI:1.6-2.5) excess cardiac deaths per 10,000 person-years (**Table 6.4**). All FPN types with at least five observed cardiac deaths were at a statistically significant increased risk of cardiac death. The SMR was substantially raised (SMR>5.0) for survivors of acute myeloid leukemia (AML), Wilms, and HL at 23.5 (95%CI:11.2-43.1), 6.5 (95%CI:4.0-10.0), and 5.6 (95%CI:3.9-7.8), respectively. Individuals likely exposed to both chest irradiation and anthracyclines were at greatest risk of cardiac death, with an SMR of 9.7 (95%CI:6.6-13.8). Survivors who were likely exposed to anthracyclines were 7.9-fold (95%CI:5.5-11.0) more at risk of cardiac death than expected, whereas survivors likely exposed to chest irradiation were 3.4-fold (95%CI:2.6-4.5) more at risk

than expected. Survivors unlikely to have been exposed to either were still 2.1-times (95%CI:1.6-2.7) more at risk of cardiac death than that expected. The SMR significantly declined (*P*trend<0.0001) and AER significantly increased (*P*trend<0.0001) with attained age (**Table 6.5**); from 0-19 to beyond 50 years age the SMR declined from 9.7-fold (95%CI:5.9-15.0) to 2.2-fold (95%CI:1.6-3.9) that expected, respectively, whilst for the same age groupings the AER rose from 0.7 (95%CI:0.4-1.1) to 12.5 (95%CI:6.1-18.9) excess cardiac deaths per 10,000 person-years, respectively (**Table 6.4**). When assessed by treatment era, evidence of a quadratic relationship was identified (*P*quadratic=0.0238) where the SMR was higher among those treated in the 1980's than those treated in decades before or since. Compared to those diagnosed before 1970, the relative risk SMR for cardiac death was 1.6-times (95%CI:1.1.-2.5), 2.3-times (95%CI:1.4-3.8), and 1.0-times (95%CI:0.4-2.1) higher among those diagnosed in 1970-1979, 1980-1989, and 1990-2006, respectively, after adjusting for age at diagnosis, attained age, FPN type, and sex (**Table 6**).

Overall, the cumulative mortality for cardiac death was 5.0% at 60 years follow-up compared to 3.5% expected (**Figure 6.1**). Among the FPN types, the cumulative mortality was greatest for survivors of Wilms and HL; the two cumulative mortality curves ran parallel to one another, with the cumulative mortality beginning to increase at 20 years follow-up for HL survivors and at 25 years follow-up for Wilms survivors (**Figure 6.2**). When assessed by likely treatment the cumulative mortalities were significantly different (*P*<0.0001); compared to the expected cumulative mortality of 0.2% at 35 years follow-up, the cumulative mortality for those likely to have been exposed to both chest irradiation and anthracyclines was 2.0% (**Figure 6.3**). Survivors likely exposed to anthracyclines or likely treated with chest irradiation had a cumulative mortality

of 0.7% and 0.6% at 35 years follow-up, respectively, which was higher than the 0.1% and 0.2% expected, respectively. The cumulative mortality for those unlikely to have been treated with chest irradiation or anthracyclines was more gradual, reaching 0.5% at 35 years follow-up.

Specific Types of Cardiac Mortality

Of the 182 cardiac deaths observed, there were 97 IHD, 52 CM/HF, 8 valvular disease, 5 arrhythmias, 2 pericardial disease, and 18 other cardiac deaths (**Table 6.7**). The SMRs for IHD, CM/HF, valvular, arrhythmia, pericardial, and other cardiac deaths were as follows, respectively: 2.5 (95%CI:2.1-3.1), 5.9 (95%CI:4.4-7.7), 3.6 (95%CI:1.6-7.2), 3.4 (95%CI:1.1-8.0), 8.0 (95%CI:1.0-29.0), and 8.3 (95%CI:4.9-13.1). When assessed by attained age, cardiomyopathy accounted for 60% of the excess cardiac mortality among those aged 5-19 years at death (**Table 6.8**). Among those aged 20-29 years and 30-39 years at death, 86.7% and 80.4% of the excess cardiac deaths, respectively, were due to IHD and CM/HF combined. From 40 years onwards, IHD deaths accounted for the majority of the excess cardiac deaths. Due to the fact that IHD and CM/HF accounted for over 80% of all cardiac deaths, we consider only these two specific cardiac outcomes separately.

Ischemic Heart Disease Mortality

The cumulative mortality of IHD deaths increased steadily until approximately 45 years follow-up, at which point there was a steep increase, ultimately reaching 3.8% at 65 years follow-up which was 1.0% higher than that expected (**Figure 6.1**). The SMR for IHD death was highest for survivors of Wilms (SMR:5.3,95%CI:2.7-9.5) and HL (SMR:4.6,95%CI:2.8-7.0) (**Table 6.4**). Survivors of CNS tumors (excluding PNET), NHL, and 'other' FPN types that did not conform

to one of the twelve FPN types analyzed also had a statistically significant elevated risk of IHD death. For individuals likely exposed to both chest irradiation and anthracyclines, the risk of IHD death was 7.6-fold (95%CI:3.1-8.2) that expected. Survivors likely exposed to anthracyclines or likely exposed to chest irradiation had similar risks for IHD death, with SMRs of 3.1 (95%CI:2.1-4.1) and 3.0 (95%CI:2.1-4.1), respectively. Nonetheless, survivors who were unlikely to have been treated with either still remained at an increased risk of IHD death (SMR:1.9,95%CI:1.4-2.6) compared to that expected. As attained age increased, the SMR declined significantly (*P*trend=0.0011) and AER increased significantly (*P*trend<0.0001) (**Table 6.5**); beyond 50 years age survivors remained over two-times (SMR:2.1,95%CI:1.3-3.8) more at risk than expected, which equated to 10.0 (95%CI:4.2-15.8) excess IHD deaths per 10,000 person-years (**Table 6.4**). There was no evidence of an effect in relation to treatment era for IHD deaths (**Table 6.5**).

Cardiomyopathy and Heart Failure Mortality

At 65 years follow-up, the cumulative mortality for CM/HF deaths was 0.5% compared to 0.3% expected (**Figure 6.1**). All FPN types with at least five observed CM/HF deaths were found to be at a substantially higher risk of CM/HF death (SMR>5.0) than that expected (**Table 6.4**); survivors of AML, NHL, and Wilms were greatest at risk, with 66.0-times (95%CI:28.5-130.0), 10.2-times (95%CI:3.7-22.2), and 8.0-times (95%CI:2.6-18.8) the number of expected CM/HF deaths, respectively. When assessed by likely treatment, survivors likely exposed to anthracyclines were at greatest risk of CM/HF death compared to that expected with a SMR of 13.9 (95%CI:8.7-21.1). Similarly, survivors likely exposed to both chest irradiation and anthracyclines were 13.6-times (95%CI:7.4-22.8) more at risk of CM/HF death. Individuals likely exposed to chest irradiation (SMR:3.1,95%CI:1.2-6.8) or unlikely to have been treated

with either (SMR:2.3,95%CI:1.1-4.2) were also at a statistically significant higher risk of CM/HF death than that expected. A decrease in multiplicative risk of CM/HF death with attained age, compared to that expected, was not observed (*P*trend=0.8121) (**Table 6.6**). With regards to treatment era, evidence of a quadratic relationship was found for both SMRs (*P*quadratic<0.0001) and AERs (*P*quadratic=0.0016). When the AERs were plotted for each year of diagnosis, the number of excess CM/HF deaths was found to be stable among those treated up to approximately 1970, at which point the number of excess deaths began to sharply increase, ultimately peaking in the mid-1980s (**Figure 6.4**). After further adjusting the AERs by age at diagnosis, attained age, FPN type, and sex, survivors diagnosed from 1970-1979, 1980-1989, and 1990-2006 had 13.9-(95%CI:1.1-168.5), 28.9-times (95%CI:2.4-354.6), 4.5-times (95%CI:0.3-69.4) the excess CM/HF deaths compared to survivors diagnosed before 1970, respectively (**Table 6.6, Figure 6.4**).

Discussion

With the most reported cardiac deaths in one study and 73,565 person-years among those aged over 40 years, this study provides more reliable and unbiased findings on cardiac mortality than has been available previously. Given our numbers, length of follow-up, wide calendar period of diagnosis, and population-based design, we have been able to determine cardiac mortality overall and for specific cardiac subgroups beyond 50 years age, and also investigate the impact of treatment era. In doing so, this study adds 207,077 person-years and 53 additional cardiac deaths to our previous largest study assessing cardiac mortality[13]. Furthermore, this study expands upon and addresses many of the limitations of previous work from the United States and Nordic countries, adding an additional 283,424 person-years and at least 25 cardiac deaths (definition of cardiac death differs between studies - our study is more restrictive) to the latest study from the United States[14,15] and a further 289,410 person-years and at least 61 cardiac deaths (definition of cardiac death differs between studies - our study is more restrictive) to the latest findings from the Nordic countries[16].

Cardiac mortality estimates in this cohort were elevated at three-times that expected, which is lower than results previously reported by a large cohort that used a similar definition for cardiac mortality[14]. However, this variation is likely due to the fact that the BCCSS has more follow-up time and the SMR declines substantially with attained age. The risk of cardiac death remained elevated beyond 50 years age and the number of excess cardiac deaths was also observed to increase significantly with age, with 13 excess deaths occurring beyond 50 years age per 10,000 person-years. This finding corresponds with our previous work, which found that the principal causes-of-death, accounting for excess number of deaths observed, were second primary cancers

and circulatory diseases as our cohort of childhood cancer survivors ages[7]. When the cumulative mortality for cardiac deaths was assessed, the curve did not plateau up to 70 years age; in fact, the difference in cumulative mortality between childhood cancer survivors and the general population appeared to increase with age. The fact that excess cardiac mortality is observed decades after treatment stresses the very long-term effects of childhood cancer and its treatment and the need for primary and secondary cardiac prevention[17].

Although previous studies have suggested that overall mortality in five-year survivors has decreased for survivors treated in more recent decades[16,18–21], only one study has been able to demonstrate a reduction in deaths from non-cancer causes[16]. To our knowledge, the present study is the first study to not only satisfactorily assess whether cardiac-specific mortality has changed over time, but also show a quadratic relationship where excess cardiac deaths were greatest for those diagnosed in the 1980s. A quadratic relationship was also found for CM/HF deaths, where the number of excess deaths began to increase in the 1970s, peaked in the mid-1980s, and then subsequently declined among those most recently diagnosed. This quadratic relationship corresponds closely with the introduction of anthracycline chemotherapy, which has been shown to increase the risk of dilated cardiomyopathy[22–24] and congestive heart failure[17]. The fact that the excess risk of cardiac death was greatest among those diagnosed in the 1980s suggests that measures to reduce cardiotoxicity through modified treatment and improved monitoring may be having a beneficial effect. Nonetheless, reassessment is necessary in order to determine whether this reduction in excess mortality persists for those more recently diagnosed with increased follow-up.

Finally, this study confirms the increased cardiovascular risks associated with thoracic radiotherapy and anthracycline exposure, individually and in combination, which has been previously observed[22,23,25–30].

Limitations

A potential limitation of our study is the lack of detailed radiotherapy and chemotherapy information, which precluded any examination of dose-response patterns of treatment exposures in relation to cardiac mortality risk. In order to assess some aspects of treatment, a proxy was used which was based upon type of cancer and year of diagnosis. Although this study has established relationships between likely treatment exposure and the risk of cardiac outcomes, the proxy variable proposed is likely too crude to aid in risk stratification. Additionally, clinical opinion on this treatment likelihood variable is likely to vary depending on institution, experience, and other factors, and thus the assumptions made when developing this proxy may not be tenable. Another possible limitation of this study is that our classification of cardiac deaths relied on the underlying cause-of-death as listed on the death certificate, which has been previously shown to have imperfect accuracy[31–34]. Despite the fact that there is possible misclassification, it is more likely that we have under-ascertained cardiac deaths and thus underestimated the risk of cardiac death among childhood cancer survivors, as these individuals are more likely to be coded as having a neoplastic-related death due to their previous medical history[35].

Conclusions

Among five-year survivors of childhood cancer treated in Britain, the excess mortality from cardiac disease is significantly increased beyond age 50. The greatest excess risk overall, and for CM/HF in particular, was observed in those diagnosed from 1980-1989 and suggests that initiatives to reduce cardiotoxicity among those treated more recently may be having a measurable impact. These findings should provide useful evidence for risk stratification and updating follow-up guidelines.

	Diagnosed <1975	Diagnosed ≥1975
Unlikely Exposed to Either Chest Irradiation or Anthracyclines	Leukemia (including AML) CNS (excluding PNET) Heritable retinoblastoma Non-heritable retinoblastoma Soft tissue sarcoma Other	CNS (excluding PNET) Heritable retinoblastoma Non-heritable retinoblastoma Other
Likely Exposed to Chest Irradiation & Unlikely Exposed to Anthracyclines	CNS PNET Hodgkin lymphoma Non-Hodgkin lymphoma Neuroblastoma Wilms Bone sarcoma	CNS PNET
Likely Exposed to Anthracyclines & Unlikely Exposed to Chest Irradiation		Leukemia (including AML) Bone sarcoma Soft tissue sarcoma
Likely Exposed to Both Chest Irradiation & Anthracyclines		Hodgkin lymphoma Non-Hodgkin lymphoma Neuroblastoma Wilms

Table 6.1: Treatment likelihood as defined by first primary neoplasm diagnostic group and year of diagnosis
Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia

	International Classification of Diseases (ICD) revision (calendar years)					
Cause of Death	**ICD-5 (1940-49)**	**ICD-6 (1950-57)**	**ICD-7 (1958-67)**	**ICD-8 (1968-78)**	**ICD-9 (1979-2000)**	**ICD-10 (2001-09)**
All Cardiac	58a-c, 90a-b, 91a-c, 92-95, 111b-c, 199, 200a(1)	401, 402.1, 410-416, 420-422, 430-434, 440-443	401, 402.1, 410-416, 420-422, 430-434, 440-443	391, 392.0, 393-398, 402, 404, 410-414, 420-429	391, 392.0, 393-398, 402, 404, 410-414, 416.1-9, 420-429	I01, I02.0, I05-I09, I11, I13, I20-I25, I27.1-9, I30-I52
Cardiomyopathy/ Heart Failure	58c, 93a-b, 93c(2-3), 93d, 111b-c, 200a(1)	401.2, 415, 422.0, 422.2, 431, 434.1-2	401.2, 415, 422.0, 422.2, 431, 434.1-2	391.2, 422, 425, 427.0, 427.1, 428	391.2, 398.0, 422, 425, 428, 429.0, 429.1, 429.3	I01.2, I09.0, I11.0, I13.0, I13.2, I40-I43, I50, I51.4-5, I51.7
Valvular Heart Disease	92a, 92b(1), 92c	421	421	394.9, 395.9, 396.9, 397.0, 424	424	I34-I39
Rheumatic Valvular Heart Disease	58b, 92b(2)	401.1, 410-414	401.1, 410-414	391.1, 394.0, 395.0, 396.0, 397.9	391.1, 394-397	I01.1, I05-I08, I09.1
Ischemic Heart Disease	93c(1), 94a, 94b	420, 422.1	420, 422.1	410-414	410-414, 429.7	I20-I25
Arrhythmias	199	433.0-1	433.0-1	427.2-9	426-427	I44-49
Pericardial Disease	58a, 90a-b	401.0, 432	401.0, 432	391.0, 393, 420, 423	391.0, 393, 420, 423	I01.0, I09.2, I30-I32
Other Cardiac	91a-c, 95	401.3, 402.1, 416, 430, 433.2, 434.0, 434.3, 440-443	401.3, 402.1, 416, 430, 433.2, 434.0, 434.3-4, 440-443	391.9, 392.0, 398, 402, 404, 421, 426, 429	391.8-9, 392.0, 389.9, 402, 404, 416.1-9, 421, 429.2, 429.4-6, 429.8-9	I01.8-9, I02.0, 109.8-9, I11.9, I13.1, I13.9, I27.1-9, I33, I51.0-3, I51.6, I51.8-9, I52

Table 6.2:International Classification of Diseases categorizations and sub-categorizations for cardiac causes-of-death as used in the analysis.

Patient Characteristic	Cardiac Death	%	Other Death	%	Total	%
Overall	182	4.1	4,301	95.9	4,483	100.0
Sex						
Male	116	4.4	2,519	95.6	2,635	100.0
Female	66	3.6	1,782	96.4	1,848	100.0
First Primary Neoplasm Type						
CNS (excluding PNET)	32	2.4	1,304	97.6	1,336	100.0
CNS PNET	5	1.5	336	98.5	341	100.0
Leukemia (excluding AML)	17	1.5	1,086	98.5	1,103	100.0
AML	10	12.2	72	87.8	82	100.0
Hodgkin Lymphoma	34	10.1	301	89.9	335	100.0
Non-Hodgkin Lymphoma	17	13.0	114	87.0	131	100.0
Neuroblastoma	4	2.8	140	97.2	144	100.0
Non-Heritable Retinoblastoma	2	6.5	29	93.5	31	100.0
Heritable Retinoblastoma	4	2.9	135	97.1	139	100.0
Wilms	20	10.9	164	89.1	184	100.0
Bone Sarcoma	9	4.5	189	95.5	198	100.0
Soft Tissue Sarcoma	12	4.7	241	95.3	253	100.0
Other	16	7.8	190	92.2	206	100.0
Age at Diagnosis						
Mean (Standard Deviation)	7.8	4.6	7.3	4.4	7.3	4.4
0-4 years	63	3.8	1,599	96.2	1,662	100.0
5-9 years	46	3.4	1,309	96.6	1,355	100.0
10-14 years	73	5.0	1,393	95.0	1,466	100.0
Treatment Era						
1940-1969	79	5.9	1,254	94.1	1,333	100.0
1970-1979	49	3.9	1,202	96.1	1,251	100.0
1980-1989	43	4.6	898	95.4	941	100.0
1990-2006	11	1.1	947	98.9	958	100.0
Likely Treatment						
Unlikely Exposed to Either Chest Irradiation or Anthracyclines	54	6.3	806	93.7	860	100.0
Likely Exposed to Chest Irradiation & Unlikely Exposed to Anthracyclines	35	3.0	1,135	97.0	1,170	100.0
Likely Exposed to Anthracyclines & Unlikely Exposed to Chest Irradiation	31	8.9	317	91.1	348	100.0
Likely Exposed to Both Chest Irradiation & Anthracyclines	62	2.9	2,047	97.1	2,109	100.0
Years Follow-Up						
Mean (Standard Deviation)	31.4	14.0	16.4	12.9	17.0	13.3
5-9 years	10	0.5	2,048	99.5	2,058	100.0
10-19 years	31	2.9	1,030	97.1	1,061	100.0
20-29 years	43	7.8	505	92.2	548	100.0
30-39 years	45	10.7	377	89.3	422	100.0
40-49 years	34	12.3	243	87.7	277	100.0
50-59 years	17	16.3	87	83.7	104	100.0
60+ years	2	11.8	15	88.2	17	100.0
Attained Age						
Mean (Standard Deviation)	39.2	14.7	23.7	13.4	24.3	13.8
5-9 years	1	0.2	415	99.8	416	100.0
10-19 years	19	1.0	1,815	99.0	1,834	100.0
20-29 years	33	3.3	972	96.7	1,005	100.0
30-39 years	43	8.0	493	92.0	536	100.0
40-49 years	36	9.8	330	90.2	366	100.0
50-59 years	32	13.4	206	86.6	238	100.0
60+ years	18	20.5	70	79.5	88	100.0

Table 6.3: Study characteristics of the British Childhood Cancer Survivor Study

Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia

		Overall Cardiac Mortality			Ischemic Heart Disease Mortality			Cardiomyopathy/Heart Failure Mortality		
	Person-Years	**O/E**	**SMR (95%CI)**	**AER (95%CI)**	**O/E**	**SMR (95%CI)**	**AER (95%CI)**	**O/E**	**SMR (95%CI)**	**AER (95%CI)**
Overall	620,758	182/53.1	3.4 (2.9,4.0)	2.1 (1.6,2.5)	97/38.2	2.5 (2.1,3.1)	0.9 (0.6,1.3)	52/8.9	5.9 (4.4,7.7)	0.7 (0.5,0.9)
Sex										
Male	336,802	116/42.2	2.7 (2.3,3.3)	2.2 (1.6,2.8)	71/31.6	2.2 (1.8,2.8)	1.2 (0.7,1.7)	27/6.6	4.1 (2.7,6.0)	0.6 (0.3,0.9)
Female	283,955	66/10.9	6.0 (4.7,7.7)	1.9 (1.4,2.5)	26/6.6	4.0 (2.6,5.8)	0.7 (0.3,1.0)	25/2.3	10.9 (7.0,16.0)	0.8 (0.5,1.1)
*P*heterogeneity			<0.0001	0.5574		0.0180	0.1132		0.0006	0.4067
First Primary Neoplasm Type										
CNS (excluding PNET)	124,750	32/13.9	2.3 (1.6,3.3)	1.5 (0.6,2.3)	20/10.4	1.9 (1.2,3.0)	0.8 (0.1,1.5)	4/2.0	2.0 (0.5,5.0)	0.2 (-0.2,0.5)
CNS PNET	18,699	5/1.5	3.3 (1.1,7.6)	1.9 (-0.5,4.2)	4/1.1	3.7 (1.0,9.5)	1.6 (-0.5,3.7)	1/0.3	3.7 (0.1,20.5)	0.4 (-0.7,1.4)
Leukemia (excluding AML)	145,237	17/4.4	3.9 (2.3,6.2)	0.9 (0.3,1.4)	3/2.2	1.4 (0.3,4.0)	0.1 (-0.2,0.3)	10/1.4	7.2 (3.5,13.3)	0.6 (0.2,1.0)
AML	13,029	10/0.4	23.5 (11.2,43.1)	7.3 (2.6,12.1)	1/0.2	4.3 (0.1,24.0)	0.6 (-0.9,2.1)	8/0.1	66.0 (28.5,130.0)	6.0 (1.8,10.3)
Hodgkin Lymphoma	42,600	34/6.1	5.6 (3.9,7.8)	6.6 (3.9,9.2)	21/4.6	4.6 (2.8,7.0)	3.9 (1.7,6.0)	6/0.9	6.7 (2.5,14.6)	1.2 (0.1,2.3)
NHL	30,343	17/4.1	4.2 (2.4,6.6)	4.3 (1.6,6.9)	8/3.1	2.6 (1.1,5.1)	1.6 (-0.2,3.4)	6/0.6	10.2 (3.7,22.2)	1.8 (0.2,3.4)
Neuroblastoma	28,500	4/1.7	2.4 (0.7,6.2)	0.8 (-0.6,2.2)	1/1.2	0.9 (0.0,4.8)	-0.1 (-0.7,0.6)	1/0.3	3.3 (0.1,18.1)	0.2 (-0.4,0.9)
Non-Heritable Retinoblastoma	26,167	2/2.8	0.7 (0.1,2.6)	-0.3 (-1.4,0.8)	2/2.1	0.9 (0.1,3.4)	-0.0 (-1.1,1.0)	0/0.4	0	-0.2 (-0.2,-0.2)
Heritable Retinoblastoma	20,162	4/1.9	2.1 (0.6,5.4)	1.0 (-0.9,3.0)	4/1.4	2.9 (0.8,7.4)	1.3 (-0.6,3.2)	0/0.3	0	-0.1 (-0.1,-0.1)
Wilms	51,519	20/3.1	6.5 (4.0,10.0)	3.3 (1.6,5.0)	11/2.1	5.3 (2.7,9.5)	1.7 (0.5,3.0)	5/0.6	8.0 (2.6,18.8)	0.8 (-0.0,1.7)
Bone Sarcoma	21,798	9/3.1	2.9 (1.3,5.4)	2.7 (-0.0,5.4)	5/2.4	2.1 (0.7,4.9)	1.2 (-0.8,3.2)	2/0.4	4.7 (0.6,16.9)	0.7 (-0.6,2.0)
Soft Tissue Sarcoma	42,062	12/4.8	2.5 (1.3,4.3)	1.7 (0.1,3.3)	7/3.6	1.9 (0.8,4.0)	0.8 (-0.4,2.0)	5/0.7	7.1 (2.3,16.7)	1.0 (-0.0,2.1)
Other	55,891	16/5.3	3.0 (1.7,4.9)	1.9 (0.5,3.3)	10/3.9	2.6 (1.2,4.8)	1.1 (-0.0,2.2)	4/0.8	4.7 (1.3,12.1)	0.6 (-0.1,1.3)
*P*heterogeneity			<0.0001	<0.0001		0.0286	0.0522		<0.0001	0.0002
Age at Diagnosis										
0-4 years	291,564	63/14.9	4.2 (3.2,5.4)	1.6 (1.1,2.2)	26/9.9	2.6 (1.7,3.9)	0.6 (0.2,0.9)	22/3.1	7.1 (4.4,10.7)	0.6 (0.3,1.0)
5-9 years	163,195	46/13.0	3.5 (2.6,4.7)	2.0 (1.2,2.8)	24/9.1	2.6 (1.7,3.9)	0.9 (0.3,1.5)	14/2.4	5.9 (3.2,9.9)	0.7 (0.3,1.2)
10-14 years	165,999	73/25.2	2.9 (2.3,3.6)	2.9 (1.9,3.9)	47/19.2	2.4 (1.8,3.2)	1.7 (0.9,2.5)	16/3.4	4.7 (2.7,7.6)	0.8 (0.3,1.2)
*P*trend			0.0292	0.0286		0.7305	0.9789		0.2074	0.6909
Treatment Era										
<1970	135,884	79/35.6	2.2 (1.8,2.8)	3.2 (1.9,4.5)	62/28.8	2.2 (1.7,2.8)	2.4 (1.3,3.6)	4/3.7	1.1 (0.3,2.7)	0.0 (-0.3,0.3)
1970-1979	152,278	49/10.7	4.6 (3.4,6.0)	2.5 (1.6,3.4)	26/6.9	3.8 (2.5,5.6)	1.3 (0.6,1.9)	16/2.4	6.5 (3.7,10.6)	0.9 (0.4,1.4)
1980-1989	155,375	43/4.7	9.1 (6.6,12.3)	2.5 (1.6,3.3)	6/2.1	2.9 (1.1,6.2)	0.3 (-0.1,0.6)	28/1.7	16.7 (11.1,24.1)	1.7 (1.0,2.4)
1990-2006	177,221	11/2.1	5.2 (2.6,9.4)	0.5 (0.1,0.9)	3/0.4	7.1 (1.5,20.6)	0.1 (-0.0,0.3)	4/1.0	3.9 (1.1,10.0)	0.2 (-0.1,0.4)
*P*trend			0.1363	0.8254		0.9152	0.0994		0.1231	0.7405

Table 6.4: Standardized mortality ratios and absolute excess risks per 10,000 person-years for overall cardiac mortality, ischemic heart disease mortality, and cardiomyopathy/heart failure mortality, by potential explanatory factors

Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia, SMR: standardized mortality ratio, AER: absolute excess risk, CI: confidence intervals

		Overall Cardiac Mortality			Ischemic Heart Disease Mortality			Cardiomyopathy/Heart Failure Mortality		
	Person-Years	**O/E**	**SMR (95%CI)**	**AER (95%CI)**	**O/E**	**SMR (95%CI)**	**AER (95%CI)**	**O/E**	**SMR (95%CI)**	**AER (95%CI)**
Likely Treatment										
Unlikely Exposed to Either Chest Irradiation	264,651	62/29.7	2.1 (1.6,2.7)	1.2 (0.6,1.8)	42/22.2	1.9 (1.4,2.6)	0.7 (0.3,1.2)	10/4.4	2.3 (1.1,4.2)	0.2 (-0.0,0.4)
Likely Exposed to Chest Irradiation & Unlikely Exposed to Anthracyclines	83,072	54/15.8	3.4 (2.6,4.5)	4.6 (2.9,6.3)	37/12.5	3.0 (2.1,4.1)	2.9 (1.5,4.4)	6/1.9	3.1 (1.2,6.8)	0.5 (-0.1,1.1)
Likely Exposed to Anthracyclines & Unlikely Exposed to Chest Irradiation	176,477	35/4.4	7.9 (5.5,11.0)	1.7 (1.1,2.4)	6/1.9	3.1 (1.2,6.8)	0.2 (-0.0,0.5)	22/1.6	13.9 (8.7,21.1)	1.2 (0.6,1.7)
Likely Exposed to Both Chest Irradiation & Anthracyclines	96,558	31/3.2	9.7 (6.6,13.8)	2.9 (1.8,4.0)	12/1.6	7.6 (4.0,13.4)	1.1 (0.4,1.8)	14/1.0	13.6 (7.4,22.8)	1.3 (0.6,2.1)
*P*heterogeneity			<0.0001	0.0001		0.0014	0.0001		<0.0001	0.0005
Attained Age										
5-19 years	243,035	20/2.1	9.7 (5.9,15.0)	0.7 (0.4,1.1)	1/0.1	8.0 (0.2,44.6)	0.0 (-0.0,0.1)	12/1.2	9.7 (5.0,16.9)	0.4 (0.2,0.7)
20-29 years	195,584	33/4.2	7.8 (5.4,11.0)	1.5 (0.9,2.0)	12/1.2	10.0 (5.2,17.5)	0.6 (0.2,0.9)	16/1.9	8.6 (4.9,14.0)	0.7 (0.3,1.1)
30-39 years	108,573	43/8.5	5.1 (3.7,6.8)	3.2 (2.0,4.4)	19/5.4	3.5 (2.1,5.5)	1.3 (0.5,2.0)	16/1.9	8.5 (4.9,13.8)	1.3 (0.6,2.0)
40-49 years	51,869	36/15.4	2.3 (1.6,3.2)	4.0 (1.7,6.2)	24/12.3	2.0 (1.3,2.9)	2.3 (0.4,4.1)	3/1.9	1.6 (0.3,4.6)	0.2 (-0.4,0.9)
50-59 years	17,552	32/14.8	2.2 (1.5,3.1)	9.8 (3.5,16.1)	25/12.4	2.0 (1.3,3.0)	7.2 (1.6,12.7)	4/1.3	3.0 (0.8,7.7)	1.5 (-0.7,3.8)
60+ years	4,144	18/8.2	2.2 (1.3,3.5)	23.7 (3.6,43.8)	16/6.8	2.3 (1.3,3.8)	22.2 (3.2,41.1)	1/0.7	1.5 (0.0,8.3)	0.8 (-3.9,5.5)
*P*trend			<0.0001	<0.0001		0.0011	<0.0001		0.8121	0.0871

Table 6.4 (*continued*): Standardized mortality ratios and absolute excess risks per 10,000 person-years for overall cardiac mortality, ischemic heart disease mortality, and cardiomyopathy/heart failure mortality, by potential explanatory factors

Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia, SMR: standardized mortality ratio, AER: absolute excess risk, CI: confidence intervals

	Overall Cardiac Mortality		Ischemic Heart Disease Mortality		Cardiomyopathy/Heart Failure Mortality	
	RR: SMR (95%CI)	**EMR (95%CI)**	**RR: SMR (95%CI)**	**EMR (95%CI)**	**RR: SMR (95%CI)**	**EMR (95%CI)**
Sex						
Male	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Female	2.2 (1.6,3.0)	0.9 (0.6,1.3)	1.8 (1.1,2.8)	0.6 (0.3,1.1)	2.7 (1.5,4.6)	1.3 0.7,2.6)
*P*heterogeneity	<0.0001	0.5574	0.0180	0.1132	0.0006	0.4067
First Primary Neoplasm Type						
CNS (excluding PNET)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
CNS PNET	1.4 (0.6,3.6)	1.3 (0.3,5.2)	1.9 (0.7,5.6)	2.0 (0.4,10.2)	1.9 (0.2,16.7)	2.5 (0.1,70.2)
Leukemia (excluding AML)	1.7 (0.9,3.0)	0.6 (0.2,1.4)	0.7 (0.2,2.4)	0.1 (0.0,5.5)	3.7 (1.2,11.7)	3.8 (0.5,31.2)
AML	10.2 (5.0,20.7)	5.1 (2.1,12.3)	2.2 (0.3,16.6)	0.8 (0.1,11.5)	33.5 (10.1,111.2)	38.3 (4.6,316.7)
Hodgkin Lymphoma	2.4 (1.5,3.9)	4.5 (2.2,9.4)	2.4 (1.3,4.4)	5.0 (1.7,14.4)	3.4 (1.0,12.1)	7.6 (0.8,68.7)
NHL	1.8 (1.0,3.2)	2.9 (1.2,7.0)	1.3 (0.6,3.0)	2.1 (0.5,8.9)	5.2 (1.5,18.4)	11.3 (1.3,100.0)
Neuroblastoma	1.0 (0.4,2.9)	0.6 (0.1,3.4)	0.4 (0.1,3.3)	*NA*	1.7 (0.2,14.8)	1.5 (0.0,49.0)
NH-Retinoblastoma	0.3 (0.1,1.3)	*NA*	0.5 (0.1,2.1)	*NA*	*NA*	*NA*
H-Retinoblastoma	0.9 (0.3,2.6)	0.7 (0.1,5.1)	1.5 (0.5,4.4)	1.7 (0.3,9.7)	*NA*	*NA*
Wilms	2.8 (1.6,4.9)	2.3 (1.0,5.0)	2.8 (1.3,5.8)	2.2 (0.7,7.2)	4.1 (1.1,15.2)	5.4 (0.6,50.0)
Bone Sarcoma	1.2 (0.6,2.6)	1.8 (0.6,6.0)	1.1 (0.4,2.9)	1.5 (0.2,10.5)	2.4 (0.4,13.0)	4.6 (0.3,65.3)
Soft Tissue Sarcoma	1.1 (0.6,2.1)	1.2 (0.4,3.6)	1.0 (0.4,2.4)	1.0 (0.2,6.2)	3.6 (1.0,13.5)	6.5 (0.7,60.7)
Other	1.3 (0.7,2.4)	1.3 (0.5,3.4)	1.3 (0.6,2.9)	1.4 (0.4,5.5)	2.4 (0.6,9.6)	3.6 (0.3,37.4)
*P*heterogeneity	<0.0001	<0.0001	0.0655	0.0003	<0.0001	0.0002
Age at Diagnosis						
0-4 years	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
5-9 years	0.8 (0.6,1.2)	1.2 (0.7,2.1)	1.0 (0.6,1.7)	1.6 (0.7,4.0)	0.8 (0.4,1.6)	1.1 (0.5,2.4)
10-14 years	0.7 (0.5,1.0)	1.7 (1.1,2.8)	0.9 (0.6,1.5)	3.0 (1.4,6.6)	0.7 (0.3,1.3)	1.2 (0.5,2.6)
*P*trend	0.0292	0.0286	0.7305	0.0068	0.2074	0.6909

Table 6.5: Relative risks of the standardized mortality ratio and excess mortality ratios per 10,000 person-years estimated using a univariate model, by potential explanatory factors

Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia, RR: relative risks, SMR: standardized mortality ratio, EMR: excess mortality ratio, CI: confidence intervals, NA: not possible to reliably calculate due to very small numbers

	Overall Cardiac Mortality		Ischemic Heart Disease Mortality		Cardiomyopathy/Heart Failure Mortality	
	RR: SMR (95%CI)	**EMR (95%CI)**	**RR: SMR (95%CI)**	**EMR (95%CI)**	**RR: SMR (95%CI)**	**EMR (95%CI)**
Treatment Era						
<1970	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1970-1979	2.1 (1.4,2.9)	0.8 (0.5,1.3)	1.7 (1.1,2.8)	0.5 (0.3,1.0)	6.1 (2.0,18.3)	*NA*
1980-1989	4.1 (2.8,6.0)	0.8 (0.5,1.3)	1.3 (0.6,3.1)	0.1 (0.0,0.4)	15.6 (5.5,44.4)	*NA*
1990-2006	2.4 (1.3,4.4)	0.2 (0.1,0.4)	3.3 (1.0,10.4)	0.1 (0.0,0.2)	3.6 (0.9,14.6)	*NA*
*P*trend	<0.0001	<0.0001	0.0184	<0.0001	<0.0001	0.7405
Attained Age						
5-19 years	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
20-29 years	0.8 (0.5,1.4)	2.0 (1.1,3.7)	1.2 (0.2,9.6)	15.3 (1.5,157.0)	0.9 (0.4,1.9)	1.6 (0.7,3.8)
30-39 years	0.5 (0.3,0.9)	4.3 (2.3,8.0)	0.4 (0.1,3.3)	34.9 (3.4,357.1)	0.9 (0.4,1.9)	2.9 (1.3,6.8)
40-49 years	0.2 (0.1,0.4)	5.4 (2.5,11.4)	0.2 (0.0,1.8)	62.9 (5.8,682.3)	0.2 (0.0,0.6)	0.5 (0.0,11.5)
50-59 years	0.2 (0.1,0.4)	13.3 (5.9,29.8)	0.3 (0.0,1.9)	199.0 (18.6,2131.5)	0.3 (0.1,1.0)	3.4 (0.7,17.0)
60+ years	0.2 (0.1,0.4)	32.1 (12.1,85.3)	0.3 (0.0,2.2)	615.5 (56.0,6762.8)	0.2 (0.0,1.2)	1.8 (0.0,678.7)
*P*trend	<0.0001	<0.0001	0.0011	<0.0001	0.0005	0.0871

Table 6.5 (*continued*): Relative risks of the standardized mortality ratio and excess mortality ratios per 10,000 person-years estimated using a univariate model, by potential explanatory factors
Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia, RR: relative risks, SMR: standardized mortality ratio, EMR: excess mortality ratio, CI: confidence intervals, NA: not possible to reliably calculate due to very small number

	Overall Cardiac Mortality		Ischemic Heart Disease Mortality		Cardiomyopathy/Heart Failure Mortality	
	RR: SMR (95%CI)	**EMR (95%CI)**	**RR: SMR (95%CI)**	**EMR (95%CI)**	**RR: SMR (95%CI)**	**EMR (95%CI)**
Sex						
Male	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Female	2.2 (1.6,3.0)	1.0 (0.7,1.6)	1.9 (1.2,3.0)	0.7 (0.3,1.3)	3.0 (1.7,5.2)	1.5 (0.8,2.9)
*P*heterogeneity	<0.0001	0.8306	0.0099	0.2246	0.0002	0.2179
First Primary Neoplasm Type						
CNS (excluding PNET)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
PNET	1.2 (0.5,3.2)	0.9 (0.2,5.4)	1.9 (0.6,5.5)	1.7 (0.2,12.8)	1.7 (0.2,15.0)	3.8 (0.2,61.0)
Leukemia (excluding AML)	0.7 (0.4,1.4)	0.8 (0.3,1.8)	0.4 (0.1,1.5)	0.2 (0.0,5.1)	1.7 (0.5,5.4)	3.2 (0.4,23.6)
AML	5.8 (2.8,12.1)	7.6 (3.2,18.1)	1.6 (0.2,12.4)	2.3 (0.2,23.2)	19.2 (5.7,64.8)	39.8 (5.5,289.6)
Hodgkin Lymphoma	2.7 (1.7,4.5)	4.1 (2.0,8.3)	2.5 (1.4,4.7)	3.8 (1.4,10.1)	3.8 (1.0,13.6)	4.9 (0.5,45.8)
NHL	2.0 (1.1,3.6)	3.0 (1.3,6.6)	1.4 (0.6,3.3)	2.1 (0.6,7.0)	5.4 (1.5,19.2)	13.8 (1.8,106.1)
Neuroblastoma	0.7 (0.2,2.1)	0.8 (0.2,3.0)	0.4 (0.1,3.2)	0.5 (0.0,9.1)	1.2 (0.1,10.7)	2.2 (0.1,38.4)
NH-Retinoblastoma	0.2 (0.1,1.0)	0.1 (0.0,3.1)	0.5 (0.1,2.1)	0.5 (0.0,5.0)	*NA*	*NA*
H-Retinoblastoma	0.7 (0.2,2.0)	0.4 (0.0,4.7)	1.4 (0.4,4.5)	1.6 (0.2,10.1)	*NA*	*NA*
Wilms	1.7 (0.9,3.1)	1.9 (0.8,4.3)	2.2 (1.0,5.1)	2.8 (0.8,9.6)	2.5 (0.7,9.9)	5.0 (0.6,41.7)
Bone Sarcoma	1.4 (0.6,2.9)	1.6 (0.5,4.9)	1.1 (0.4,2.9)	0.9 (0.1,8.4)	2.6 (0.5,14.2)	6.2 (0.5,71.1)
Soft Tissue Sarcoma	1.1 (0.5,2.1)	1.0 (0.3,2.9)	1.0 (0.4,2.5)	0.9 (0.2,4.5)	3.5 (0.9,13.2)	8.0 (1.0,65.0)
Other	1.1 (0.6,2.1)	1.0 (0.4,2.8)	1.2 (0.6,2.6)	1.2 (0.3,4.6)	2.1 (0.5,8.3)	3.6 (0.4,36.0)
*P*heterogeneity	<0.0001	<0.0001	0.0286	0.0522	0.0003	0.0002
Age at Diagnosis						
0-4 years	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
5-9 years	0.7 (0.4,1.1)	0.7 (0.4,1.2)	0.9 (0.5,1.8)	1.0 (0.4,2.8)	0.7 (0.3,1.4)	0.7 (0.3,1.6)
10-14 years	0.6 (0.4,0.9)	0.5 (0.3,0.9)	0.8 (0.4,1.6)	1.0 (0.4,2.8)	0.5 (0.2,1.1)	0.5 (0.2,1.2)
*P*trend	0.0090	0.0251	0.5539	0.9789	0.0666	0.0986
Treatment Era						
<1970	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1970-1979	1.6 (1.1,2.5)	1.3 (0.7,2.4)	1.5 (0.9,2.6)	1.0 (0.5,2.2)	8.9 (2.1,37.8)	13.9 (1.1,168.5)
1980-1989	2.3 (1.4,3.8)	1.8 (0.9,3.4)	0.8 (0.3,2.0)	0.3 (0.1,1.3)	18.2 (3.9,84.2)	28.9 (2.4,354.6)
1990-2006	1.0 (0.4,2.1)	0.6 (0.2,1.4)	1.0 (0.3,3.8)	0.4 (0.1,1.9)	3.7 (0.6,23.3)	4.5 (0.3,69.4)
*P*trend	0.1363	0.8254	0.9152	0.0994	0.1231	0.3453
Attained Age						
5-19 years	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
20-29 years	0.8 (0.5,1.5)	1.9 (1.0,3.6)	1.3 (0.2,9.9)	11.1 (1.3,98.3)	0.9 (0.4,2.0)	1.6 (0.7,3.6)
30-39 years	0.6 (0.3,1.0)	3.7 (1.8,7.3)	0.4 (0.1,3.2)	20.8 (2.3,186.9)	1.0 (0.4,2.3)	2.9 (1.2,7.2)
40-49 years	0.3 (0.2,0.6)	5.6 (2.5,12.7)	0.2 (0.0,1.7)	29.0 (3.0,284.1)	0.4 (0.1,1.4)	*NA*
50-59 years	0.4 (0.2,0.8)	16.7 (6.5,43.5)	0.2 (0.0,2.0)	89.6 (8.9,901.6)	2.2 (0.5,10.4)	21.3 (3.1,147.8)
60+ years	0.4 (0.2,1.0)	44.8 (14.3,140.6)	0.3 (0.0,2.6)	258.0 (23.4,2849.1)	2.0 (0.1,26.7)	*NA*
*P*trend	0.0055	<0.0001	0.0267	<0.0001	0.8121	0.0591

Table 6.6: Relative risks of the standardized mortality ratio and excess mortality ratios per 10,000 person-years estimated using a multivariate model, adjusting for sex, first primary neoplasm type, age at diagnosis, treatment era, and attained age

Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia, RR: relative risks, SMR: standardized mortality ratio, EMR: excess mortality ratio, CI: confidence intervals, NA: not possible to reliably calculate due to very small number

	O/E	SMR (95%CI)	AER (95%CI)
Overall	182/53.1	3.4 (2.9,4.0)	2.1 (1.6,2.5)
Ischemia Heart Disease	97/38.2	2.5 (2.1,3.1)	0.9 (0.6,1.3)
Cardiomyopathy/Heart Failure	52/8.9	5.9 (4.4,7.7)	0.7 (0.5,0.9)
Valvular	8/2.2	3.6 (1.6,7.2)	0.1 (0.0,0.2)
Arrhythmia	5/1.5	3.4 (1.1,8.0)	0.1 (0.0,0.1)
Pericardial	2/0.2	8.0 (1.0,29.0)	0.0 (0.0,0.1)
Other Cardiac	18/2.2	8.3 (4.9,13.1)	0.3 (0.1,0.4)

Table 6.7: Standardized mortality ratios and absolute excess risks per 10,000 person-years for deaths due to all cardiac causes and cardiac-specific causes

Abbreviations: O: observed, E: expected, SMR: standardized mortality ratio, CI: confidence interval, AER: absolute excess risk

	Attained Age (% cardiac)					
	5-19 years	**20-29 years**	**30-39 years**	**40-49 years**	**50-59 years**	**60+ years**
Ischemic Heart Disease	4.9%	37.5%	39.5%	57.1%	73.0%	93.6%
Cardiomyopathy/Heart Failure	60.0%	49.2%	40.9%	5.3%	15.5%	3.4%
Valvular Heart Disease	-1.0%	2.1%	4.5%	17.3%	3.3%	-3.3%
Arrhythmias	9.4%	5.4%	2.0%	-0.9%	-0.6%	-1.1%
Pericardial Disease	5.5%	-0.2%	2.8%	-0.3%	-0.3%	-0.3%
Other Cardiac	21.3%	5.9%	10.3%	21.6%	9.0%	7.7%
All Cardiac	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%

Table 6.8: Excess deaths of each cardiac subgroup as a proportion of the total excess cardiac deaths, by attained age

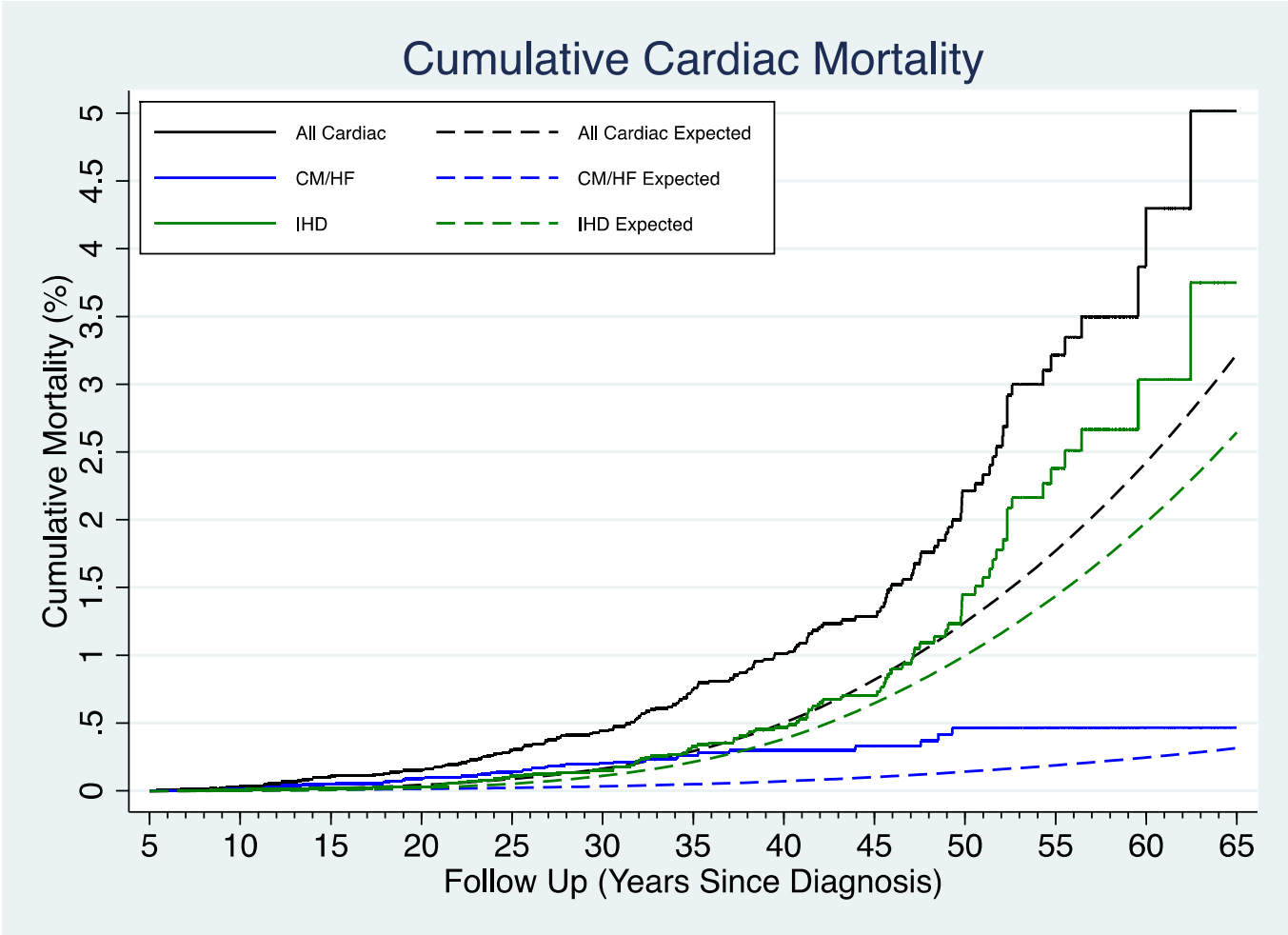

Figure 6.1: Cumulative mortality of all cardiac causes, ischemic heart disease causes, and cardiomyopathy/heart failure causes among childhood cancer survivors compared to that expected in the general population, by follow-up (years since diagnosis)
Abbreviations: CM/HF: cardiomyopathy/heart failure, IHD: ischemic heart disease

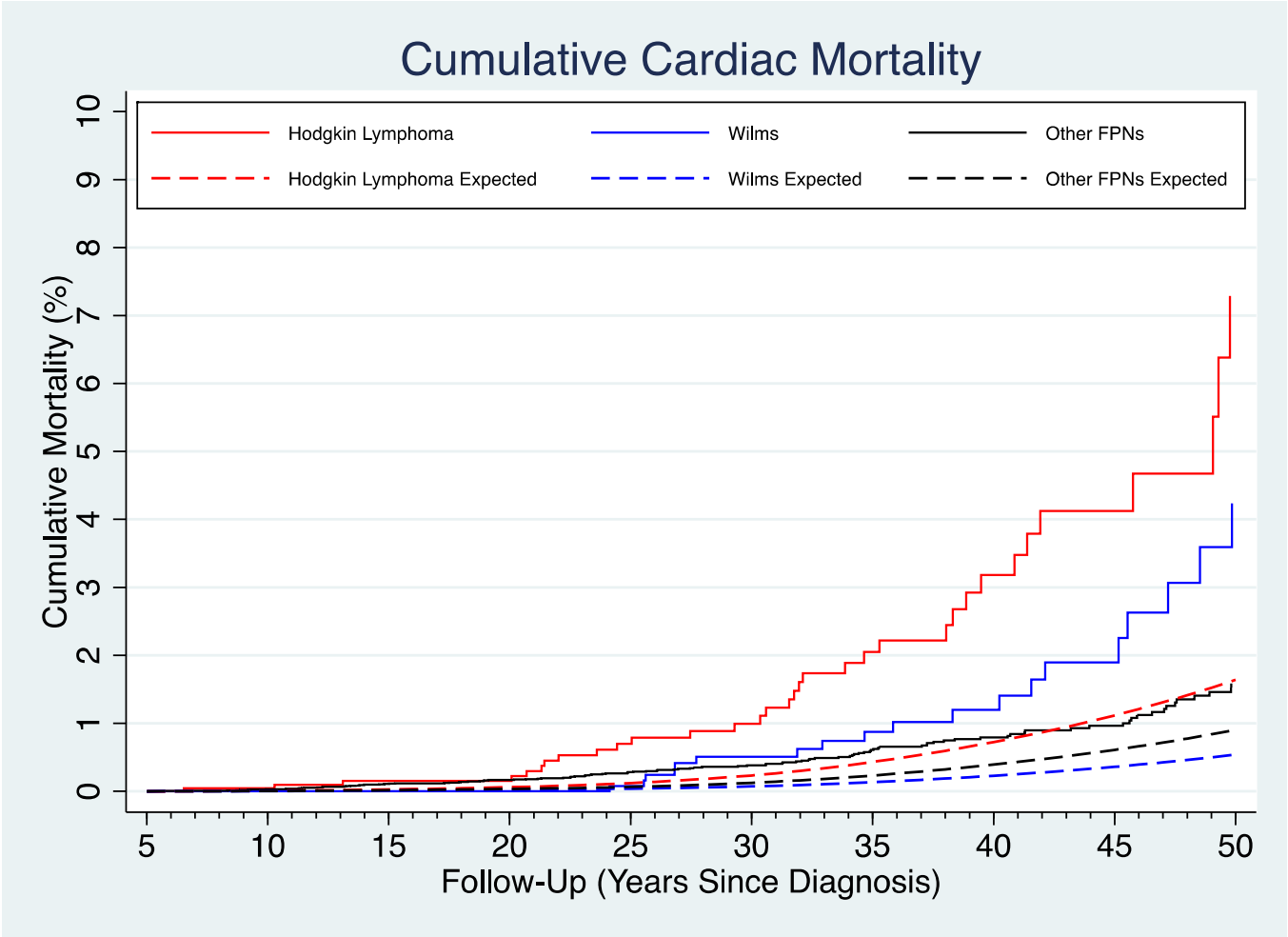

Figure 6.2: Cumulative mortality for cardiac death by first primary neoplasm diagnostic groups, by follow-up (years since diagnosis), compared to that expected overall
Abbreviation: FPN: first primary neoplasm

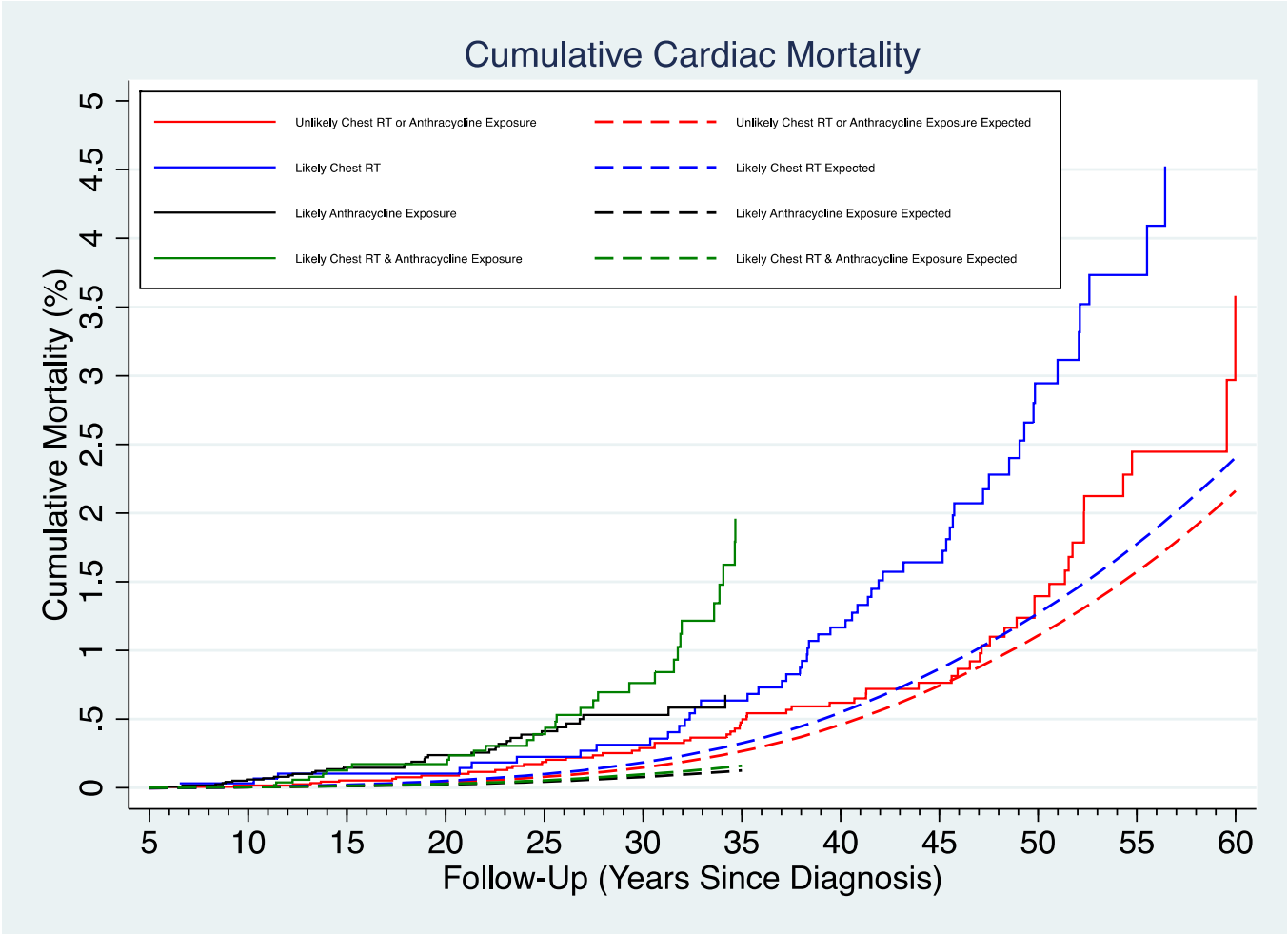

Figure 6.3: Cumulative mortality for cardiac death by likely treatment, by follow-up (years since diagnosis), compared to that expected overall
Abbreviations: RT: radiotherapy

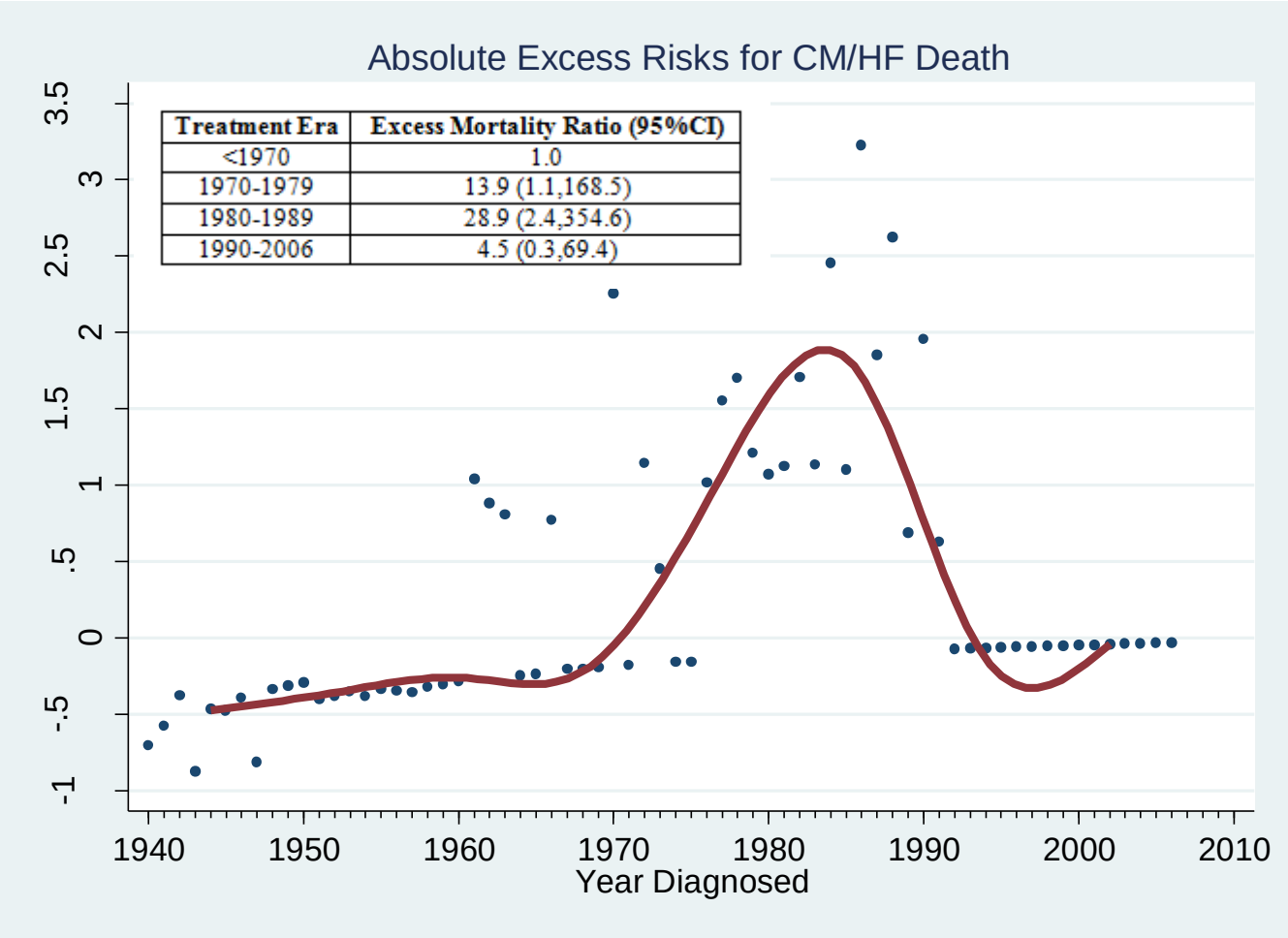

Figure 6.4: The graph depicts the point estimates of cardiomyopaty/heart failure absolute excess risks per 10,000 person-years for each year of diagnosis.
The curve was produced by calculating cross medians and then using the cross medians to fit a spline[11]. The table depicts the excess mortality ratio for cardiomyopathy/heart failure deaths, which was calculated in a multivariate Poisson model adjusting for sex, age at diagnosis, first primary neoplasm type, and attained age.
Abbreviation: CM/HF: cardiomyopathy/heart failure, CI: confidence intervals

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CHAPTER 7

STUDY 5:

Population-based long-term respiratory mortality among 235,434 five-year survivors of cancer diagnosed before age 40 years

Abstract

Purpose: Exposure to radiation and/or chemotherapy can compromise respiratory function in survivors of childhood, teenage, and young adult cancers, and thus it is important to monitor late respiratory outcomes. We investigated the risk of long-term respiratory mortality among cancer survivors diagnosed before age 40 using two of the largest population-based cohorts of survivors: the British Childhood Cancer Survivor Study (BCCSS) and Teenage and Young Adult Cancer Survivor Study (TYACSS).

Material and Methods: The BCCSS comprises 34,489 five-year survivors of childhood cancer diagnosed in Great Britain between 1940-2006 before the age of 15. The TYACSS includes 200,945 five-year survivors of cancers diagnosed from age 15 to 39 between 1971-2006 in England and Wales. Standardized mortality ratios (SMRs) and absolute excess risks (AERs) were used.

Results: Overall, 164 and 1,067 respiratory deaths were observed for the BCCSS and TYACSS cohorts, respectively, which was 6.8- and 1.7-times that expected. By respiratory subgroups, the SMR was greatest for deaths related to pneumonitis (SMR:16.9) and fibrosis (SMR:13.8) in the BCCSS, and pneumonitis (SMR:2.1) and pneumonia (SMR:2.0) for TYACSS. Those diagnosed with leukemia, lung, or CNS tumors in the TYACSS cohort had the greatest risks, whereas CNS, leukemia, and germ cell tumor survivors were at greatest risk in the BCCSS. For all respiratory deaths, the SMRs declined and AERs increased with attained age. When assessed by era, the AER significantly declined with more recent decades in both the BCCSS (*P*trend=0.0153) and TYACSS (*P*trend=0.0258).

Conclusions: Among five-year survivors of cancer diagnosed before age 40, the excess respiratory mortality was significantly increased beyond 50 years attained age. However, it is reassuring that the AERs are decreasing among those treated more recently.

Introduction

Although survival from childhood, teenage, and young adult cancer has improved substantially over recent decades, with approximately 80% of those diagnosed now surviving at least five years[1,2], increased survival comes at a cost as curative treatments are often associated with adverse late effects. Previous research has found that specific types of both radiotherapy and chemotherapy have a significant impact on respiratory function and thoracic development[3]. Direct irradiation to the chest and lungs can cause developmental abnormalities of the thoracic cage, as well as short-term treatment-induced lung disease, presenting as pneumonitis, and interstitial lung injury and long-term damage, manifesting as fibrosis[3]. Only specific chemotherapy drugs are currently known to cause late respiratory effects, with conditions usually presenting acutely, there is the potential for significant morbidity and mortality in the long-term[3].

Due to the fact that this population of survivors is growing and that these individuals likely have a large proportion of their expected lives ahead, it is crucial to investigate respiratory late effects in order to better understand risk factors and identify vulnerable subgroups of survivors. Although previous literature has assessed respiratory morbidity among childhood cancer survivors[4], to our knowledge, this is the first study to focus specifically on respiratory mortality. Previous studies have been prevented from satisfactorily undertaking detailed analyses relating to this outcome because of limited follow-up time and small numbers of respiratory deaths. In addition, previous studies have not been able to satisfactorily address the risk of respiratory mortality beyond 50 years age nor determine whether long-term respiratory mortality has improved for survivors treated in more recent treatment eras.

In this study we assessed the long-term risks of respiratory mortality among 235,434 five-year survivors of cancer diagnosed before the age of 40 years using the British Childhood Cancer Survivor Study (BCCSS) and Teenage and Young Adult Cancer Survivor Study (TYACSS). The BCCSS and TYACSS are the largest studies to date to assess long-term mortality in survivors of childhood, teenage, and young adult cancers, and thus provide a valuable evidence base for mortality risks among these individuals.

Material and Methods

Study Population

This study investigates two of the largest population-based cohorts of survivors: the British Childhood Cancer Survivor Study (BCCSS)[5] and Teenage and Young Adult Cancer Survivor Study (TYACSS)[6]. The BCCSS comprises 34,489 five-year survivors of childhood cancer diagnosed under the age of 15 years in Great Britain from 1940-2006. The cohort was identified using the National Registry of Childhood Tumors, which has a high estimated level of ascertainment (~99%)[7]. All first primary neoplasms (FPN) were classified using the International Classification of Childhood Cancer[8]. Similarly, TYACSS includes 200,945 five-year survivors of teenage and young adult cancers diagnosed from 1971-2006 between the ages of 15-39. The cohort was established in cooperation with the Office for National Statistics (ONS). As cancer incidence rates take up to five years after the end of a given calendar year to reach 100%[9], it is expected that ascertainment for this cohort is essentially complete as the upper limit for diagnosis inclusion was 2006 and this cohort was established in 2012. Teenage and young adult FPNs were classified using the categories proposed by Birch et al., which was been slightly modified to evaluate finer groupings[10]. Also, for analyses that combined the BCCSS and TYACSS cohort, FPNs were classified using the proposed categories by Birch et al[10]. The National Research Ethics Committee and Confidentiality Advisory Group gave ethical and legal approval for the BCCSS and TYACSS cohorts.

Death Ascertainment

The BCCSS and TYACSS cohorts were linked with the Health and Social Care Information Centre in order to ascertain each survivor's vital and embarkation status. An attempt was then made for each death to obtain the death certificate and underlying cause-of-death as coded by the ONS (England and Wales) and General Registrar Office (Scotland) using the relevant *International Classification of Diseases* (ICD). A respiratory death was defined by using the 'diseases of the respiratory system' chapter of the relevant ICD version; ICD codes were further sub-categorized into clinically relevant groups for analysis, specifically: pneumonia, chronic lower respiratory disease, fibrosis, pneumonitis, and other respiratory (**Table 7.1**). Follow-up for respiratory mortality commenced at five-year survival and continued until the first occurrence of emigration, death, or February 28, 2014.

Statistical Analyses

To investigate the risk of premature mortality among survivors compared to that expected from the general population, standardized mortality ratios (SMRs) and absolute excess risks (AERs) were calculated using standard cohort techniques[11]. The SMR was defined as the ratio of the observed over expected number of respiratory deaths. The AER was defined as the observed minus the expected number of respiratory deaths divided by person-years at risk multiplied by 10,000. Expected numbers were calculated by multiplying the person-years for each sex-specific, age-specific (five-year bands), and calendar year-specific (one-year bands) stratum by the corresponding respiratory mortality rate for the population of England and Wales and then summing across the strata[12]. In order to evaluate the simultaneous effect of demographic and cancer-related factors, multivariate Poisson regression models for the SMRs and AERs were

used, adjusting for sex, FPN type, age at cancer diagnosis, treatment era, and attained age. If the results from the univariate and multivariate models were similar, suggesting little confounding, then the univariate findings were reported in terms of SMRs. If the results from the univariate and multivariate models differed (changing from statistical significant to statistically insignificant or statistically insignificant to statistically significant), then the multivariate results were reported in terms of relative risks (RR) for the SMRs and excess mortality ratios for the AERs. Likelihood-ratio tests within Poisson regression models were used to test for heterogeneity or trend.

Cumulative mortality, as a function of follow-up or attained age, was estimated by using the stcompet command in Stata[13]. Causes-of-death other than the one under study were treated as competing risks[14]. Log rank tests were used to test for heterogeneity in the cumulative mortality between different groups.

All analyses were completed using Stata 12.1[13], where the criterion for statistical significance was a two-sided *P*-value less than 0.05.

Results

British Childhood Cancer Survivor Study

Overall Respiratory Mortality

The BCCSS cohort was followed up for a total of 620,758 person-years from five-year survival. The mean follow-up was 18.0 years (range:0.0-68.7) and mean attained age was 29.6 years (range:5.5-85.6) at the study exit date. Of the 4,483 deaths observed, 164 (3.7%) were due to respiratory causes (**Table 7.2)**. Over half of the respiratory deaths were observed in survivors of central nervous system (CNS) tumors, including CNS primitive neuroectodermal tumors (PNET). The mean follow-up and attained age at time of respiratory death was 24.7 years and 32.0 years, respectively; this was higher than the mean follow-up and attained age for non-respiratory causes-of-death.

Survivors of childhood cancer were 6.8-times (95%CI:5.8-7.9) more at risk of respiratory death than expected in the general population; this equated to 2.3 (95%CI:1.8-2.7) excess respiratory deaths per 10,000 person-years (**Table 7.3**). All FPN types with at least five observed events were found to be significantly more at risk of respiratory death than that expected; however, the risk was substantially raised (SMR>5.0) for survivors of CNS PNET (SMR:22.6,95%CI:12.7-37.4), acute myeloid leukemia (AML) (SMR:12.6,95%:2.6-36.7), CNS (excluding PNET) (SMR:11.4,95%CI:8.8-14.4), and germ cell tumors (SMR:10.5,95%CI:4.5-20.8). As attained age increased, the SMR significantly declined (*P*trend<0.0001) and the AER significantly increased (*P*trend<0.0001) (**Table 7.4**); at 5-19 years age, the SMR was 14.5 (95%CI:5.8-29.9) and the AER was 1.7 (0.3-3.1), whilst beyond 50 years age the SMR and AER were 2.6 (95%CI:1.7-3.9) and 6.8 (95%CI:2.4-11.3), respectively. When assessed by treatment era, the number of excess

respiratory deaths declined significantly (*P*trend<0.0001) (**Table 7.4**); after adjusting for sex, age at diagnosis, FPN type, and attained age, survivors diagnosed from 1990-2006 experienced 40% (SMR RR:0.4,95%CI:0.2-0.8) of the excess respiratory deaths observed among those diagnosed before 1970 (**Table 7.5, Figure 7.1**).

Specific Types of Respiratory Mortality

Of the 164 respiratory deaths observed, there were 77 pneumonia, 18 pneumonitis, 15 fibrosis, 11 chronic lower respiratory disease (excluding asthma), and 43 other respiratory deaths (**Table 7.3**); the corresponding SMRs were 8.2 (95%CI:6.5-10.2), 16.9 (95%CI:10.0-26.8), 13.8 (95%CI:7.7-22.8), 1.8 (95%CI:0.9-3.2), and 6.5 (95%CI:4.7-8.8), respectively. As nearly half of the respiratory deaths observed were due to pneumonia, further analyses will only be discussed for this respiratory-specific subgroup. However, it is worth noting that 13/18 (72.2%) of the pneumonitis deaths occurred CNS (excluding PNET) survivors, which equated to a 53.8-fold (95%CI28.6-92.0) increased risk compared to that expected (**Table 7.3**).

Survivors of CNS PNET, germ cell tumors, and CNS tumors (excluding PNET) were at greatest risk of death due to pneumonia, with SMRs of 36.1 (95%CI:17.3-66.4), 16.9 (95%CI:5.5-39.4), and 15.8 (95%CI:11.1-21.9), respectively (**Table 7.3**). The SMRs significantly declined as attained age increased (*P*trend=0.0006) (**Table 7.4**), although 4.4 (95%CI:1.3-7.5) excess pneumonia deaths were observed beyond 50 years age. With regards to treatment era, a significant decline (*P*trend<0.0001) in excess pneumonia deaths was observed among those more recently diagnosed (**Table 7.4**). Compared to survivors diagnosed before 1970, those diagnosed

in 1990-2006 experienced 10% (EMR:0.1,95%CI:0.0-0.3) of the excess pneumonia deaths, after adjusting for sex, FPN type, age at diagnosis, and attained age (**Table 7.5**).

Teenage and Young Adult Cancer Survivor Study

Overall Respiratory Mortality

From five-year survival, the TYACSS cohort was followed up for a total of 2,867,878 person-years. The mean follow-up was 14.3 years (range:0.0-38.2) and attained age was 51.0 years (range:20.0-82.7) at the study exit date. By the study exit date, 34,188 (17.0%) teenage and young adult (TYA) survivors had died; of these, 1,067 (3.1%) were due to respiratory causes (**Table 7.6**). Over half of the respiratory deaths were observed among survivors diagnosed between the ages of 35-39. The mean follow-up and attained was 21.9 years and 55.2, respectively, at time of respiratory death; this was again higher than the corresponding means for non-respiratory deaths.

Overall, TYA survivors were 70% (SMR:1.7,95%CI:1.6-1.8) more likely to die from a respiratory cause than expected from the general population, which equated to 1.5 (95%CI:1.3-1.7) excess respiratory deaths per 10,000 person-years (**Table 7.7**). Survivors of CNS PNET, AML, leukemia (excluding AML), and lung cancer were at greatest risk of respiratory death, with SMRs of 6.8 (95%CI:1.4-19.9), 5.7 (95%CI:2.9-9.9), 4.8 (95%CI:3.1-7.1), and 4.2 (95%CI:2.8-6.0), respectively. As attained age increased, the SMRs significantly declined (*P*trend<0.0001) and AER significantly increased (*P*trend=0.0002) (**Table 7.8**). When assessed by treatment era, a significant decline (*P*trend=0.0258) in AER was observed where those diagnosed during 2000-2006 had 60% (EMR:0.6,95%CI:0.3-1.0) of the excess respiratory deaths observed among those

diagnosed during 1971-1979, after adjusting for sex, FPN type, age at diagnosis, and attained age (**Table 7.8**).

Specific Types of Respiratory Mortality

When the 1,067 respiratory deaths were assessed by the respiratory-specific subgroups, there were 390 pneumonia, 388 chronic lower respiratory (excluding asthma), 74 fibrosis, 48 pneumonitis, and 167 other respiratory deaths (**Table 7.7**). The SMR was greatest for pneumonitis and pneumonia deaths at 2.1 (95%CI:1.6-2.8) and 2.0 (1.8-2.3), respectively. TYA survivors, however, were at a significantly increased risk of death from pulmonary fibrosis (SMR:1.7,95%CI:1.4-2.2), chronic lower respiratory (SMR:1.3,95%CI:1.2-1.5), and other respiratory deaths (SMR:1.8,95%CI:1.6-2.1) as well.

When risk of pneumonia death was assessed by FPN type, survivors of CNS PNET (SMR:18.7,95%CI:3.9-54.7), bone tumors (SMR:5.2,95%CI:2.2-10.2), and leukemia (excluding AML) (SMR:5.1,95%CI:2.3-9.6), had a substantially high increased risk (SMR>5.0) of pneumonia death compared to that expected (**Table 7.7**). As attained age increased, the SMR significantly declined (*P*trend<0.0001) (**Table 7.8**); from 20-29 years age to beyond 70 years age the SMR declined from 6.7 (95%CI:2.9-13.2) to 1.0 (95%CI:0.7-1.5). With regards to treatment era, the number of excess pneumonia deaths significantly declined among those treated more recently (*P*trend=0.0020) (**Table 7.9**). After adjusting for sex, FPN type, age at diagnosis, and attained age, survivors diagnosed from 2000-2006 experienced 50% (EMR:0.5,95%CI:0.2-1.0) of the excess pneumonia deaths observed among those diagnosed from 1971-1979 (**Table 7.8**).

For chronic lower respiratory disease deaths, survivors of lung cancer were at greatest risk with an SMR of 4.8 (95%CI:2.7-7.8), followed by survivors of leukemia (excluding AML) (SMR:3.0,95%CI:1.1-6.6), and Hodgkin lymphoma (SMR:2.3,95%CI:1.6-3.1) (**Table 7.7**). The SMR significantly decreased (*P*trend=0.0001) and AER significantly increased (*P*trend=0.0024) with attained age (**Table 7.9**). Furthermore, when treatment era was assessed, survivors diagnosed more recently were significantly less likely to die from chronic lower respiratory disease (*P*trend=0.0003). Individuals diagnosed from 2000-2006 experienced 10% of the excess chronic lower respiratory deaths observed among those diagnosed from 1971-1979, after adjusting for sex, FPN type, age at diagnosis, and attained age (**Table 7.8**).

Females were 2.7-times (95%CI:1.5-4.9) more likely to die from a fibrosis-related death than males, after adjusting for FPN type, age at diagnosis, treatment era, and attained age (**Table 7.8**). Hodgkin lymphoma survivors were the only FPN type with a statistically significant increased risk of fibrosis death, which was 6.7-fold (95%CI:4.0-10.4) that expected from the general population (**Table 7.7**). As attained age increased, the SMR significantly declined (*P*trend<0.0001) (**Table 7.9**). The SMR was 39.2 (95%CI:4.7-141.5) among individuals aged 20-29 years and declined to 0.6 (95%CI:0.2-1.4) among individuals aged over 60 years (**Table 7.7**). There was no evidence that the excess numbers of lung fibrosis deaths varied across era of treatment (*P*trend=0.9868) (**Table 7.8**).

Finally, for pneumonitis deaths, CNS (excluding PNET), leukemia (excluding AML), and head and neck cancer survivors had the greatest risk of death, with SMRs of 12.3 (95%CI:7.4-19.2), 13.7 (95%CI:2.8-39.9), and 8.8 (95%CI:2.9-20.6), respectively (**Table 7.7**). Again, the SMR

significantly decreased as attained age increased (*P*trend=0.0078) (**Table 7.9**). With regards to treatment era, a significant decrease in excess pneumonitis deaths among individuals more recently treated was not observed (*P*trend=0.6839) (**Table 7.8**).

Comparing the BCCSS and TYACSS

In order to assess the effect of age at diagnosis on the risk of respiratory mortality, the BCCSS and TYACSS cohorts were combined. When cumulative mortality was stratified by each age at diagnosis group, a significant difference was found (*P*<0.0001), where those diagnosed at an older age were found to have the highest cumulative mortality (**Figure 7.3**). However, when the effect of age at diagnosis was assessed in multivariate Poisson models adjusting for sex, FPN type, treatment era, and attained age, in fact the SMR (*P*trend<0.0001) and AER (*P*trend=0.0001) were found to significantly decline as age at diagnosis increased. Survivors diagnosed under the age of 15 years appeared to have comparable risks of respiratory death, whilst individuals aged 15-39 at diagnosis appeared to be more homogeneous.

Discussion

This is the first study to assess respiratory-specific mortality among five-year survivors of cancer who were diagnosed before the age of 40 years. Furthermore, when childhood and separately teenage and young adult cancers were assessed individually, this is the largest study to date to report on respiratory mortality in relation to each group. Previous studies from Scotland[15], Finland[16], the United States[17], and the Nordic countries[18] have assessed respiratory mortality in a portion of the age at diagnosis period utilized in this study; however, these studies had substantially less survivors, follow-up, and events, reporting only six, 15, 67, and 82 respiratory deaths, respectively. Although we have previously reported on overall respiratory mortality among childhood cancer survivors in the BCCSS[19], this updated analysis includes a further 16,509 survivors of childhood cancer and adds an additional 58 respiratory deaths, which ultimately leads to more precise risk estimates. Additionally, over 200,000 survivors of teenage and young adult cancer were included in this study. Due to our study's population-based design, large number of observed events, and long period of follow-up, this study provides the most comprehensive results for respiratory mortality among childhood, teenage, and young adult cancer survivors to date.

In relation to childhood cancer, substantial excesses in risk were observed, with survivors experiencing approximately seven-times more respiratory deaths than that expected from the general population. This finding corresponds with previous findings reported from the United States[17,20], but is substantially lower than the 34.9-fold increased risk reported from the Nordic countries[18]. A 70% increased risk of respiratory death was also observed in the TYACSS cohort. To date, few studies have addressed survivorship among teenage and young adult cancer

survivors, particularly individuals diagnosed between the ages of 22 and 39 years, with the majority of the understanding of long-term effects coming from childhood cohorts[17,21,22]. Nonetheless, our finding comparable with studies from Finland[16] and Scotland[15], which reported SMRs of 2.7 (95%CI:1.3-3.8) and 3.4 (95%CI:1.2-7.4), respectively. Excesses in respiratory death were observed to increase with attained age in both the BCCSS and TYACSS, with substantial deaths occurring even beyond 50 years age.

To date, no previous study has assessed specific types of respiratory mortality among childhood, teenage, and young adult cancer survivors, which is likely due to the limited follow-up and observed events available in previous studies. However, our study identifies appreciable excesses in risk for pneumonia, chronic lower respiratory disease, fibrosis, and pneumonitis deaths, with particular FPN types being at a particularly high risk. By investigating specific types of respiratory mortality, recommendations can be made for survivors and clinicians, which relate to disease specific outcome groups. Thus, the novel findings presented in this study will provide useful evidence for the development of more precise clinical follow-up guidelines.

In this study, survivors of CNS tumors (including PNET), germ cell tumors, and AML were found to have the greatest risk of respiratory death among childhood cancer survivors. Similarly, survivors of CNS (including PNET), leukemia (including AML), lung cancer, bone tumors, head and neck cancers, and Hodgkin lymphoma were found to be at an increased risk for at least one of the specific types of respiratory death analyzed among teenage and young adult cancer survivors. The increased risks observed in these FPN types likely relate to adverse effects of treatment as chest irradiation and chemotherapy drugs such as bleomycin, nitrosoureas,

cyclophosphamide, methotrexate, busulfan, and cytosine araboside have all been linked to late respiratory effects[23]. In particular, previous studies have found increased risks of adverse respiratory outcomes for survivors of Hodgkin lymphoma, germ cell tumors, rhabdomyosarcoma, neuroblastoma, bone tumors, and CNS, and acute lymphoblastic leukemia[23–30]. Among CNS survivors, adverse respiratory outcomes are likely due to craniospinal irradiation, which can induce pneumonitis and late restrictive lung disease[30]. Adverse respiratory outcomes are also well described in leukemia survivors, where both restrictive and obstructive lung disease have been reported[23,26]. Hodgkin lymphoma survivors have also been found to be at an increased risk of adverse respiratory outcomes, with more than 30% of survivors were reported to have asymptomatic radiographic findings or restrictive changes on respiratory function[24,25,31]. Increased risks in germ cell and bone tumor survivors also likely relates to treatment as both are treated with respiratory-toxic agents[28,29].

Due to our study's wide period of diagnosis, we also illustrated a significant decline in excess mortality due to all respiratory and pneumonia deaths among individuals more recently diagnosed for both the BCCSS and TYACSS. Additionally, teenage and young adult cancer survivors were also found to experience significantly less excess deaths due to chronic lower respiratory disease among those more recently diagnosed. Although previous reports have illustrated a decline with treatment era for non-cancer deaths[32] and non-recurrence/non-external deaths[20], this is the first study to illustrate a decline specifically for respiratory causes. This decrease in excess mortality likely relates to the dramatic decrease in the radiation-induced late respiratory toxicity due to refined techniques of radiotherapy and increased monitoring of chemotherapy-induced toxicity[23,33–35].

Finally, this study reported a significant decline in the SMRs for respiratory death as age at diagnosis increased. Compared to individuals diagnosed at the age of 0-4 years, survivors diagnosed from 5-9 and 10-14 years were each 1.2-times more likely to die from respiratory death. Conversely, survivors diagnosed between the ages of 15-39 years had 30%-50% of the excess numbers of respiratory deaths compared to those diagnosed between the ages of 0-4 years at diagnosis. This finding highlights the importance of evidence-based guidelines by age at diagnosis, as individuals diagnosed before 15 years age appear to exhibit similar increased risks to one another, which are substantially higher than those diagnosed after 15 years age. Thus, in relation to respiratory death, clinical guidelines and recommendations that encompass the entire age at diagnosis period assessed in this study are likely unacceptable as the risk is not uniform for all survivors.

Limitations

As our study determined respiratory deaths based upon the underlying cause-of-death, as coded on the death certificate, there is possible misclassification in our study as the underlying cause-of-death has been previously shown to have imperfect accuracy[36–39]. Another limitation of this study is the lack of detailed radiotherapy and chemotherapy, which prevented any examination of dose response patterns.

Conclusions

In conclusion, this large-scale, population-based study provides evidence that survivors of childhood, teenage, and young adult cancer are at an increased risk of respiratory death, compared to that expected, both overall and for specific types of respiratory death. The number of excess respiratory deaths was observed to increase significantly with attained age, with significant excesses occurring beyond 50 years age for childhood cancer survivors and beyond 60 years age for teenage and young adult cancer survivors. Nonetheless, there is evidence that there is a reduction in the excess number of respiratory deaths among individuals more recently diagnosed, which is likely due to more modern treatments, improvements in supportive care, and increased screening and detection of late effects. These findings provide unbiased and reliable estimates of respiratory mortality among childhood, teenage, and young adult cancer survivors, which provides an evidence-base on which to update clinical follow-up guidelines for childhood cancer survivors and to develop clinical follow-up guidelines in relation to teenage and young adult cancer survivors.

International Classification of Diseases (ICD) version	All Respiratory	Pneumonia	Chronic Lower Respiratory Disease	Fibrosis	Pneumonitis	Other Respiratory
ICD 7	470-527	480, 490-493	500-502, 526, 527.1	524	525	470-479,481-483, 510-523, 527.0, 527.2
ICD 8	460-519	471, 480-486	518, 490-492	*NA*	517	460-470, 472-474, 493-516, 519
ICD 9	460-519	480-486	490-492, 494, 496	495.0, 495.1, 500-505, 506.4, 508.1, 515,516.3	495.7-495.9, 506.0, 507, 508.0, 516.8, 518.3	460-478, 487, 493, 495.2-495.6, 506.1-506.3, 506.9, 508.8-508.9,510-514, 516.0-516.2, 516.9, 517, 518.0-518.2, 518.4-519.9
ICD 10	J00-J99	J12-J18	J40-J44, J47	J60.0-J63.5, J66.0, J67.0, J67.1, J68.1, J68.4, J70.0	J67.0, J67.1,J67.7-J67.9, J68.0, J69, J84.8, J95.4	J00-J11, J20-J39, J45-46, J60.0-J63.5, J63.8-J66.0, J66.1-J66.8, J67.2-J67.6, J68.1-J68.4, J68.8-68.9, J70.1-J84.1, J84.9-J95.3, J95.5-J99.8

Table 7.1 – International Classification of Diseases categorizations and sub-categorizations for respiratory causes-of-death as used in the analysis
Abbreviations: NA: not applicable

Patient Characteristic	Respiratory Death	%	Other Death	%	Total	%
Overall	164	3.7	4319	96.3	4,483	100.0
Sex						
Male	98	3.7	2537	96.3	2,635	100.0
Female	66	3.6	1782	96.4	1,848	100.0
First Primary Neoplasm Type						
CNS (excluding PNET)	68	5.3	1225	94.7	1,293	100.0
PNET	15	4.4	326	95.6	341	100.0
Leukemia (excluding AML)	23	2.1	1080	97.9	1,103	100.0
AML	3	3.7	79	96.3	82	100.0
Hodgkin Lymphoma	7	2.1	328	97.9	335	100.0
Non-Hodgkin Lymphoma	5	3.8	126	96.2	131	100.0
Neuroblastoma	6	4.2	138	95.8	144	100.0
Non-Heritable Retinoblastoma	1	3.2	30	96.8	31	100.0
Heritable Retinoblastoma	4	2.9	135	97.1	139	100.0
Wilms	7	3.8	177	96.2	184	100.0
Bone Sarcoma	1	0.5	197	99.5	198	100.0
Soft Tissue Sarcoma	11	4.3	242	95.7	253	100.0
Germ Cell Tumors	8	10.7	67	89.3	75	100.0
Other	5	2.9	169	97.1	174	100.0
Age at Diagnosis						
Mean (SD)	7.3	4.6	7.3	4.4	7.3	4.4
0-4	64	3.9	1598	96.1	1,662	100.0
5-9	43	3.2	1312	96.8	1,355	100.0
10-14	57	3.9	1409	96.1	1,466	100.0
Treatment Era						
1940-1969	61	4.6	1272	95.4	1,333	100.0
1970-1979	48	3.8	1203	96.2	1,251	100.0
1980-1989	36	3.8	905	96.2	941	100.0
1990-2006	19	2.0	939	98.0	958	100.0
Years Follow-Up						
Mean (SD)	24.7	1.1	16.7	0.2	17	13.3
5-9 years	36	1.7	2022	98.3	2,058	100.0
10-19 years	33	3.1	1028	96.9	1,061	100.0
20-29 years	33	6.0	515	94.0	548	100.0
30-39 years	32	7.6	388	91.9	422	100.0
40-49 years	21	7.6	256	92.4	277	100.0
50-59 years	8	7.7	95	91.3	104	100.0
60+ years	1	5.9	15	88.2	17	100.0
Attained Age						
Mean (SD)	32	1.2	24	0.2	24.3	13.8
5-9 years	7	1.7	409	98.3	416	100.0
10-19 years	37	2.0	1797	98.0	1,834	100.0
20-29 years	35	3.5	970	96.5	1,005	100.0
30-39 years	34	6.3	502	93.7	536	100.0
40-49 years	27	7.4	339	92.6	366	100.0
50-59 years	20	8.4	218	91.6	238	100.0
60+ years	4	4.5	84	95.5	88	100.0

Table 7.2: Study characteristics of the British Childhood Cancer Survivor Study (BCCSS)

Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia, SD: standard deviation

		All Respiratory			Pneumonia			Chronic Lower Respiratory Disease		
	Person-Years	O/E	SMR (95%CI)	AER (95%CI)	O/E	SMR (95%CI)	AER (95%CI)	O/E	SMR (95%CI)	AER (95%CI)
Overall	620,758	164/24.2	6.8 (5.8,7.9)	2.3 (1.8,2.7)	77/9.4	8.2 (6.5,10.2)	1.1 (0.8,1.4)	11/6.1	1.8 (0.9,3.2)	0.1 (-0.0,0.2)
Sex										
Male	336,802	98/14.9	6.6 (5.3,8.0)	2.5 (1.9,3.0)	48/6.1	7.9 (5.8,10.5)	1.2 (0.8,1.6)	4/3.6	1.1 (0.3,2.9)	0.0 (-0.1,0.1)
Female	283,955	66/9.3	7.1 (5.5,9.0)	2.0 (1.4,2.6)	29/3.4	8.6 (5.8,12.4)	0.9 (0.5,1.3)	7/2.5	2.8 (1.1,5.8)	0.2 (-0.0,0.3)
First Primary Neoplasm Type										
CNS (excluding PNET)	120,973	68/6.0	11.4 (8.8,14.4)	5.1 (3.8,6.5)	36/2.3	15.8 (11.1,21.9)	2.8 (1.8,3.8)	2/1.7	1.2 (0.1,4.3)	0.0 (-0.2,0.3)
PNET	18,699	15/0.7	22.6 (12.7,37.4)	7.7 (3.6,11.7)	10/0.3	36.1 (17.3,66.4)	5.2 (1.9,8.5)	0/0.1	0	-0.1 (-0.1,-0.1)
Leukemia (excluding AML)	145,237	23/2.7	8.5 (5.4,12.7)	1.4 (0.7,2.0)	10/1.1	8.9 (4.3,16.4)	0.6 (0.2,1.0)	0/0.2	0	-0.0 (-0.0,-0.0)
AML	13,029	3/0.2	12.6 (2.6,36.7)	2.1 (-0.5,4.7)	0/0.1	0	-0.1 (-0.1,-0.1)	1/0.0	41.2 (1.0,229.7)	0.7 (-0.8,2.3)
Hodgkin Lymphoma	42,600	7/2.3	3.1 (1.2,6.4)	1.1 (-0.1,2.3)	3/0.9	3.3 (0.7,9.6)	0.5 (-0.3,1.3)	0/0.6	0	-0.1 (-0.1,-0.1)
Non-Hodgkin Lymphoma	30,343	5/1.6	3.1 (1.0,7.4)	1.1 (-0.3,2.6)	2/0.6	3.3 (0.4,12.0)	0.5 (-0.5,1.4)	1/0.5	2.2 (0.1,12.2)	0.2 (-0.5,0.8)
Neuroblastoma	28,500	6/0.8	7.2 (2.6,15.7)	1.8 (0.1,3.5)	1/0.3	3.0 (0.1,16.5)	0.2 (-0.5,0.9)	1/0.2	6.0 (0.2,33.5)	0.3 (-0.4,1.0)
Non-Heritable Retinoblastoma	26,167	1/1.3	0.8 (0.0,4.3)	-0.1 (-0.9,0.6)	0/0.5	0	-0.2 (-0.2,-0.2)	0/0.4	0	-0.1 (-0.1,-0.1)
Heritable Retinoblastoma	20,162	4/0.9	4.5 (1.2,11.4)	1.5 (-0.4,3.5)	3/0.4	8.2 (1.7,23.9)	1.3 (-0.4,3.0)	0/0.2	0	-0.1 (-0.1,-0.1)
Wilms	51,519	7/1.6	4.4 (1.8,9.1)	1.1 (0.0,2.1)	1/0.7	1.5 (0.0,8.5)	0.1 (-0.3,0.4)	1/0.3	3.3 (0.1,18.4)	0.1 (-0.2,0.5)
Bone Sarcoma	21,798	1/1.4	0.7 (0.0,4.1)	-0.2 (-1.1,0.7)	0/0.5	0	-0.2 (-0.2,-0.2)	1/0.5	2.2 (0.1,12.4)	0.3 (-0.6,1.2)
Soft Tissue Sarcoma	42,062	11/2.1	5.4 (2.7,9.6)	2.1 (0.6,3.7)	5/0.8	6.5 (2.1,15.1)	1.0 (-0.0,2.0)	2/0.6	3.4 (0.4,12.2)	0.3 (-0.3,1.0)
Germ Cell Tumors	22,298	8/0.8	10.5 (4.5,20.8)	3.2 (0.8,5.7)	5/0.3	16.9 (5.5,39.4)	2.1 (0.1,4.1)	1/0.2	5.7 (0.1,31.8)	0.4 (-0.5,1.2)
Other	37,370	5/2.0	2.5 (0.8,5.8)	0.8 (-0.4,2.0)	1/0.7	1.4 (0.0,7.6)	0.1 (-0.5,0.6)	1/0.6	1.5 (0.0,8.6)	0.1 (-0.4,0.6)
Age at Diagnosis										
0-4 years	291,564	64/7.8	8.2 (6.3,10.4)	1.9 (1.4,2.5)	27/3.2	8.5 (5.6,12.3)	0.8 (0.5,1.2)	3/1.4	2.1 (0.4,6.2)	0.1 (-0.1,0.2)
5-9 years	163,195	43/6.0	7.2 (5.2,9.7)	2.3 (1.5,3.1)	21/2.4	8.8 (5.4,13.4)	1.1 (0.6,1.7)	3/1.4	2.2 (0.5,6.5)	0.1 (-0.1,0.3)
10-14 years	165,999	57/10.4	5.5 (4.1,7.1)	2.8 (1.9,3.7)	29/3.8	7.5 (5.0,10.8)	1.5 (0.9,2.2)	5/3.3	1.5 (0.5,3.5)	0.1 (-0.2,0.4)
Treatment Era										
<1970	135,884	61/14.3	4.3 (3.3,5.5)	3.4 (2.3,4.6)	35/5.2	6.7 (4.7,9.3)	2.2 (1.3,3.0)	7/5.1	1.4 (0.5,2.8)	0.1 (-0.2,0.5)
1970-1979	152,278	48/5.2	9.3 (6.8,12.3)	2.8 (1.9,3.7)	23/2.3	9.9 (6.2,14.8)	1.4 (0.7,2.0)	1/0.6	1.5 (0.0,8.6)	0.0 (-0.1,0.2)
1980-1989	155,375	36/2.9	12.4 (8.7,17.2)	2.1 (1.4,2.9)	17/1.3	13.6 (7.9,21.8)	1.0 (0.5,1.5)	1/0.2	5.0 (0.1,27.6)	0.1 (-0.1,0.2)
1990-2006	177,221	19/1.8	10.4 (6.2,16.2)	1.0 (0.5,1.5)	2/0.6	3.2 (0.4,11.6)	0.1 (-0.1,0.2)	2/0.1	28.9 (3.5,104.5)	0.1 (-0.0,0.3)
Years Follow-Up										
5-9 years	161,046	36/2.3	15.4 (10.8,21.4)	2.1 (1.4,2.8)	18/1.0	18.8 (11.1,29.6)	1.1 (0.5,1.6)	2/0.1	15.1 (1.8,54.5)	0.1 (-0.1,0.3)
10-19 years	229,665	33/4.0	8.2 (5.6,11.5)	1.3 (0.8,1.8)	13/1.8	7.4 (3.9,12.7)	0.5 (0.2,0.8)	2/0.2	9.2 (1.1,33.2)	0.1 (-0.0,0.2)
20-29 years	132,085	33/3.8	8.7 (6.0,12.2)	2.2 (1.4,3.1)	16/1.9	8.4 (4.8,13.7)	1.1 (0.5,1.7)	1/0.3	3.4 (0.1,18.7)	0.1 (-0.1,0.2)
30-39 years	66,379	32/4.4	7.2 (5.0,10.2)	4.2 (2.5,5.8)	16/2.0	7.8 (4.5,12.7)	2.1 (0.9,3.3)	0/0.9	0	-0.1 (-0.1,-0.1)
40-49 years	24,972	21/5.1	4.1 (2.5,6.3)	6.4 (2.8,10.0)	9/1.7	5.3 (2.4,10.1)	2.9 (0.6,5.3)	5/2.1	2.4 (0.8,5.6)	1.2 (-0.6,2.9)
50+ years	6,610	9/4.6	2.0 (0.9,3.8)	6.7 (-2.2,15.6)	5/1.1	4.7 (1.5,10.9)	6.0 (-0.7,12.6)	1/2.5	0.4 (0.0,2.2)	-2.2 (-5.2,0.7)
Attained Age										
5-9 years	38,220	7/0.5	14.5 (5.8,29.9)	1.7 (0.3,3.1)	3/0.2	13.7 (2.8,40.2)	0.7 (-0.2,1.6)	1/0.0	34.7 (0.9,193.2)	0.3 (-0.3,0.8)
10-19 years	204,815	37/2.9	12.7 (9.0,17.5)	1.7 (1.1,2.2)	18/1.1	15.8 (9.4,25.0)	0.8 (0.4,1.2)	0/0.1	0	-0.0 (-0.0,-0.0)
20-29 years	195,584	35/3.7	9.3 (6.5,13.0)	1.6 (1.0,2.2)	14/1.7	8.3 (4.5,13.9)	0.6 (0.3,1.0)	3/0.2	14.7 (3.0,42.9)	0.1 (-0.0,0.3)
30-39 years	108,573	34/3.7	9.2 (6.4,12.8)	2.8 (1.7,3.8)	20/2.0	10.3 (6.3,15.8)	1.7 (0.9,2.5)	1/0.3	3.6 (0.1,20.2)	0.1 (-0.1,0.2)
40-49 years	51,869	27/4.3	6.3 (4.2,9.2)	4.4 (2.4,6.3)	10/2.0	5.1 (2.4,9.4)	1.5 (0.4,2.7)	2/0.8	2.4 (0.3,8.5)	0.2 (-0.3,0.8)
50+ years	21,697	24/9.1	2.6 (1.7,3.9)	6.8 (2.4,11.3)	12/2.5	4.9 (2.5,8.5)	4.4 (1.3,7.5)	4/4.6	0.9 (0.2,2.2)	-0.3 (-2.1,1.5)

Table 7.3: Standardized mortality ratios and absolute excess risks per 10,000 person-years for overall respiratory, pneumonia, and chronic lower respiratory disease mortality, by potential explanatory factors, for the British Childhood Cancer Survivor Study

Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia, O: observed, E: expected, SMR: standardized mortality ratio, AER: absolute excess risk, CI: confidence intervals

		Fibrosis			Pneumonitis			Other Respiratory		
	Person-Years	O/E	SMR (95%CI)	AER (95%CI)	O/E	SMR (95%CI)	AER (95%CI)	O/E	SMR (95%CI)	AER (95%CI)
Overall	620,758	15/1.1	13.8 (7.7,22.8)	0.2 (0.1,0.3)	18/1.1	16.9 (10.0,26.8)	0.3 (0.1,0.4)	43/6.6	6.5 (4.7,8.8)	0.6 (0.4,0.8)
Sex										
Male	336,802	6/0.7	8.5 (3.1,18.6)	0.2 (0.0,0.3)	11/0.7	16.3 (8.1,29.1)	0.3 (0.1,0.5)	29/3.9	7.4 (5.0,10.7)	0.7 (0.4,1.1)
Female	283,955	9/0.4	23.6 (10.8,44.7)	0.3 (0.1,0.5)	7/0.4	18.1 (7.3,37.3)	0.2 (0.1,0.4)	14/2.7	5.1 (2.8,8.6)	0.4 (0.1,0.7)
First Primary Neoplasm Type										
CNS (excluding PNET)	120,973	3/0.3	10.4 (2.2,30.5)	0.2 (-0.1,0.5)	13/0.2	53.8 (28.6,92.0)	1.1 (0.5,1.6)	14/1.5	9.5 (5.2,16.0)	1.0 (0.4,1.6)
PNET	18,699	2/0.0	78.9 (9.6,285.1)	1.1 (-0.4,2.5)	0/0.0	0	-0.0 (-0.0,-0.0)	3/0.2	15.2 (3.1,44.4)	1.5 (-0.3,3.3)
Leukemia (excluding AML)	145,237	3/0.1	39.0 (8.0,113.9)	0.2 (-0.0,0.4)	1/0.2	6.3 (0.2,34.9)	0.1 (-0.1,0.2)	9/1.1	8.1 (3.7,15.4)	0.5 (0.1,0.9)
AML	13,029	2/0.0	281.0 (34.0,1015.0)	1.5 (-0.6,3.7)	0/0.0	0	-0.0 (-0.0,-0.0)	0/0.1	0	-0.1 (-0.1,-0.1)
Hodgkin Lymphoma	42,600	1/0.1	9.5 (0.2,52.7)	0.2 (-0.3,0.7)	0/0.1	0	-0.0 (-0.0,-0.0)	3/0.6	5.4 (1.1,15.7)	0.6 (-0.2,1.4)
Non-Hodgkin Lymphoma	30,343	1/0.1	12.4 (0.3,69.2)	0.3 (-0.3,0.9)	0/0.1	0	-0.0 (-0.0,-0.0)	1/0.4	2.6 (0.1,14.7)	0.2 (-0.4,0.9)
Neuroblastoma	28,500	1/0.0	29.8 (0.8,166.2)	0.3 (-0.3,1.0)	1/0.0	27.2 (0.7,151.6)	0.3 (-0.3,1.0)	2/0.3	7.7 (0.9,27.9)	0.6 (-0.4,1.6)
Non-Heritable Retinoblastoma	26,167	0/0.1	0	-0.0 (-0.0,-0.0)	0/0.1	0	-0.0 (-0.0,-0.0)	1/0.3	3.1 (0.1,17.5)	0.3 (-0.5,1.0)
Heritable Retinoblastoma	20,162	0/0.0	0	-0.0 (-0.0,-0.0)	0/0.0	0	-0.0 (-0.0,-0.0)	1/0.2	4.2 (0.1,23.2)	0.4 (-0.6,1.3)
Wilms	51,519	2/0.1	34.0 (4.1,122.8)	0.4 (-0.2,0.9)	0/0.1	0	-0.0 (-0.0,-0.0)	3/0.5	6.0 (1.2,17.5)	0.5 (-0.2,1.1)
Bone Sarcoma	21,798	0/0.1	0	-0.0 (-0.0,-0.0)	0/0.1	0	-0.0 (-0.0,-0.0)	0/0.3	0	-0.1 (-0.1,-0.1)
Soft Tissue Sarcoma	42,062	0/0.1	0	-0.0 (-0.0,-0.0)	1/0.1	11.6 (0.3,64.8)	0.2 (-0.2,0.7)	3/0.5	6.0 (1.2,17.6)	0.6 (-0.2,1.4)
Germ Cell Tumors	22,298	0/0.0	0	-0.0 (-0.0,-0.0)	1/0.0	28.1 (0.7,156.4)	0.4 (-0.4,1.3)	1/0.2	4.5 (0.1,25.1)	0.3 (-0.5,1.2)
Other	37,370	0/0.1	0	-0.0 (-0.0,-0.0)	1/0.1	12.2 (0.3,67.8)	0.2 (-0.3,0.8)	2/0.5	4.3 (0.5,15.4)	0.4 (-0.3,1.2)
Age at Diagnosis										
0-4 years	291,564	8/0.3	28.0 (12.1,55.3)	0.3 (0.1,0.5)	8/0.4	22.2 (9.6,43.8)	0.3 (0.1,0.5)	18/2.6	7.0 (4.1,11.0)	0.5 (0.2,0.8)
5-9 years	163,195	2/0.3	8.0 (1.0,28.7)	0.1 (-0.1,0.3)	4/0.3	14.6 (4.0,37.5)	0.2 (-0.0,0.5)	13/1.7	7.5 (4.0,12.9)	0.7 (0.3,1.1)
10-14 years	165,999	5/0.5	9.1 (3.0,21.3)	0.3 (0.0,0.5)	6/0.4	14.0 (5.1,30.4)	0.3 (0.0,0.6)	12/2.3	5.2 (2.7,9.1)	0.6 (0.2,1.0)
Treatment Era										
<1970	135,884	0/0.8	0	-0.1 (-0.1,-0.1)	5/0.5	10.5 (3.4,24.4)	0.3 (0.0,0.7)	14/2.7	5.2 (2.8,8.7)	0.8 (0.3,1.4)
1970-1979	152,278	8/0.2	45.9 (19.8,90.4)	0.5 (0.1,0.9)	8/0.3	30.8 (13.3,60.7)	0.5 (0.1,0.9)	8/1.8	4.5 (2.0,8.9)	0.4 (0.0,0.8)
1980-1989	155,375	5/0.1	64.0 (20.8,149.3)	0.3 (0.0,0.6)	4/0.2	21.5 (5.9,55.1)	0.2 (-0.0,0.5)	9/1.2	7.6 (3.5,14.4)	0.5 (0.1,0.9)
1990-2006	177,221	2/0.0	54.1 (6.5,195.3)	0.1 (-0.0,0.3)	1/0.1	7.1 (0.2,39.7)	0.0 (-0.1,0.2)	12/1.0	12.5 (6.4,21.8)	0.6 (0.2,1.0)
Years Follow-Up										
5-9 years	161,046	4/0.0	164.9 (44.9,422.2)	0.2 (0.0,0.5)	1/0.1	14.0 (0.4,78.2)	0.1 (-0.1,0.2)	11/1.1	9.6 (4.8,17.2)	0.6 (0.2,1.0)
10-19 years	229,665	6/0.1	100.4 (36.8,218.5)	0.3 (0.0,0.5)	3/0.2	17.3 (3.6,50.4)	0.1 (-0.0,0.3)	9/1.8	4.9 (2.2,9.3)	0.3 (0.1,0.6)
20-29 years	132,085	4/0.1	38.7 (10.6,99.2)	0.3 (-0.0,0.6)	4/0.2	20.0 (5.5,51.3)	0.3 (-0.0,0.6)	8/1.3	6.2 (2.7,12.2)	0.5 (0.1,0.9)
30-39 years	66,379	1/0.2	5.4 (0.1,29.9)	0.1 (-0.2,0.4)	7/0.2	30.1 (12.1,62.1)	1.0 (0.2,1.8)	8/1.1	7.3 (3.1,14.3)	1.0 (0.2,1.9)
40-49 years	24,972	0/0.3	0	-0.1 (-0.1,-0.1)	2/0.2	9.0 (1.1,32.4)	0.7 (-0.4,1.8)	5/0.8	6.3 (2.0,14.6)	1.7 (-0.1,3.4)
50+ years	6,610	0/0.4	0	-0.6 (-0.6,-0.6)	1/0.2	6.1 (0.2,34.1)	1.3 (-1.7,4.2)	2/0.5	4.4 (0.5,16.0)	2.3 (-1.8,6.5)
Attained Age										
5-9 years	38,220	1/0.0	174.1 (4.4,970.2)	0.3 (-0.3,0.8)	0/0.0	0	-0.0 (-0.0,-0.0)	2/0.2	9.2 (1.1,33.4)	0.5 (-0.3,1.2)
10-19 years	204,815	4/0.0	144.6 (39.4,370.3)	0.2 (0.0,0.4)	1/0.1	12.3 (0.3,68.6)	0.0 (-0.1,0.1)	14/1.5	9.3 (5.1,15.5)	0.6 (0.3,1.0)
20-29 years	195,584	7/0.1	108.4 (43.6,223.4)	0.4 (0.1,0.6)	5/0.2	25.1 (8.1,58.5)	0.2 (0.0,0.5)	6/1.6	3.8 (1.4,8.2)	0.2 (-0.0,0.5)
30-39 years	108,573	2/0.1	18.6 (2.3,67.2)	0.2 (-0.1,0.4)	3/0.2	15.8 (3.2,46.0)	0.3 (-0.1,0.6)	8/1.2	6.8 (2.9,13.3)	0.6 (0.1,1.1)
40-49 years	51,869	1/0.2	5.4 (0.1,30.1)	0.2 (-0.2,0.5)	6/0.2	26.0 (9.5,56.5)	1.1 (0.2,2.0)	8/1.0	7.7 (3.3,15.3)	1.3 (0.3,2.4)
50+ years	21,697	0/0.7	0	-0.3 (-0.3,-0.3)	3/0.3	8.6 (1.8,25.2)	1.2 (-0.3,2.8)	5/1.1	4.6 (1.5,10.8)	1.8 (-0.2,3.8)

Table 7.3 (*continued*): Standardized mortality ratios and absolute excess risks per 10,000 person-years for fibrosis, pneumonitis, and other respiratory mortality, by potential explanatory factors, for the British Childhood Cancer Survivor Study

Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia, O: observed, E: expected, SMR: standardized mortality ratio, AER: absolute excess risk, CI: confidence intervals

	All Respiratory		Pneumonia		Chronic Lower Respiratory Disease		Fibrosis		Pneumonitis		Other Respiratory	
	RR: SMR (95%CI)	EMR (95%CI)	RR: SMR (95%CI)	EMR (95%CI)	RR: SMR (95%CI)	EMR (95%CI)	RR: SMR (95%CI)	EMR (95%CI)	RR: SMR (95%CI)	EMR (95%CI)	RR: SMR (95%CI)	EMR (95%CI)
Sex												
Male	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Female	1.1 (0.8,1.5)	0.8 (0.6,1.2)	1.1 (0.7,1.7)	0.7 (0.4,1.2)	2.5 (0.7,8.6)	12.6 (0.0,136520.6)	2.8 (1.0,7.7)	1.9 (0.6,6.0)	1.1 (0.4,2.9)	0.8 (0.3,2.1)	70.7 (0.4,1.3)	0.5 (0.2,1.2)
*P*heterogeneity	0.6509	0.2519	0.7192	0.2233	0.1316	0.1728	0.0514	0.02437	0.8272	0.5891	0.2483	0.0955
First Primary Neoplasm Type												
CNS (excluding PNET)	2.1 (1.1,4.0)	2.4 (1.1,5.2)	2.4 (1.0,6.2)	2.8 (0.9,8.3)	0.3 (0.0,2.5)	0.1 (0.0,885.5)	*NA*	*NA*	4.6 (0.6,35.3)	4.9	1.6 (0.5,5.5)	1.7 (0.4,7.6)
PNET	4.2 (1.9,9.2)	3.6 (1.5,8.9)	5.6 (1.9,16.3)	5.2 (1.5,17.5)	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	2.5 (0.5,12.5)	2.5 (0.4,15.5)
Leukemia (excluding AML)	1.6 (0.8,3.2)	0.7 (0.3,1.6)	1.4 (0.5,4.0)	0.6 (0.2,2.1)	*NA*	*NA*	*NA*	*NA*	0.5 (0.0,8.6)	0.3 (0.0,6.3)	1.3 (0.4,5.0)	0.9 (0.2,4.3)
AML	2.3 (0.7,8.4)	1.0 (0.2,4.2)	*NA*	*NA*	12.2 (1.1,134.8)	2.2 (0.1,37.3)	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
Hodgkin Lymphoma	0.6 (0.2,1.5)	0.5 (0.1,1.9)	0.5 (0.1,2.1)	0.5 (0.1,3.4)	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	0.9 (0.2,4.4)	1.0 (0.1,6.7)
Non-Hodgkin Lymphoma	0.6 (0.2,1.7)	0.5 (0.1,2.3)	0.5 (0.1,2.6)	0.5 (0.0,4.3)	0.6 (0.1,7.1)	0.5 (0.0,32.8)	*NA*	*NA*	*NA*	*NA*	0.4 (0.0,4.2)	0.3 (0.0,10.7)
Neuroblastoma	1.3 (0.5,3.6)	0.9 (0.3,2.8)	0.5 (0.1,3.9)	0.2 (0.0,5.3)	1.8 (0.2,19.7)	0.9 (0.0,18.8)	*NA*	*NA*	2.3 (0.1,37.4)	1.6	1.3 (0.2,7.7)	1.0 (0.1,8.3)
Non-Heritable Retinoblastoma	0.1 (0.0,1.1)	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	0.5 (0.1,5.0)	0.4 (0.0,10.5)
Heritable Retinoblastoma	0.8 (0.3,2.6)	0.7 (0.2,3.1)	1.3 (0.3,5.3)	1.3 (0.2,6.8)	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	0.7 (0.1,6.7)	0.6 (0.0,11.7)
Wilms	0.8 (0.3,2.1)	0.5 (0.1,1.6)	0.2 (0.0,2.0)	0.1 (0.0,20.5)	1.0 (0.1,10.8)	0.4 (0.0,12.5)	*NA*	*NA*	*NA*	*NA*	1.0 (0.2,4.9)	0.8 (0.1,5.6)
Bone Sarcoma	0.1 (0.0,1.1)	*NA*	*NA*	*NA*	0.7 (0.1,7.3)	0.8 (0.0,44.3)	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
Soft Tissue Sarcoma	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Germ Cell Tumors	2.0 (0.8,4.9)	1.5 (0.5,4.4)	2.6 (0.8,9.0)	2.1 (0.5,8.5)	1.7 (0.2,18.6)	1.1 (0.1,24.2)	*NA*	*NA*	2.4 (0.2,38.6)	2.0	0.7 (0.1,7.2)	0.6 (0.0,10.3)
Other	0.5 (0.2,1.3)	0.4 (0.1,1.9)	0.2 (0.0,1.8)	0.1 (0.0,106.1)	0.5 (0.0,5.0)	0.3 (0.0,104.2)	*NA*	*NA*	1.0 (0.1,16.7)	1.1	0.7 (0.1,4.3)	0.7 (0.1,6.6)
*P*heterogeneity	<0.0001	<0.0001	<0.0001	<0.0001	0.4222	0.7460	0.0100	0.2211	0.0074	0.0036	0.5436	0.6517
Age at Diagnosis												
0-4 years	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
5-9 years	0.9 (0.6,1.3)	1.2 (0.8,1.8)	1.0 (0.6,1.8)	1.4 (0.7,2.7)	1.1 (0.2,5.2)	1.9 (0.1,36.7)	0.3 (0.1,1.3)	0.4 (0.1,2.3)	0.7 (0.2,2.2)	0.9 (0.2,3.1)	1.1 (0.5,2.2)	1.3 (0.6,3.0)
10-14 years	0.7 (0.5,1.0)	1.5 (1.0,2.2)	0.9 (0.5,1.5)	1.9 (1.0,3.4)	0.7 (0.2,3.0)	1.9 (0.1,54.0)	0.3 (0.1,1.0)	1.0 (0.3,3.4)	0.6 (0.2,1.8)	1.3 (0.4,4.0)	0.7 (0.4,1.6)	1.1 (0.5,2.7)
*P*trend	0.0271	0.0871	0.6448	0.0443	0.6183	0.6766	0.0470	0.8651	0.3833	0.7079	0.4603	0.7589
Treatment Era												
<1970	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1970-1979	2.2 (1.5,3.2)	0.8 (0.5,1.3)	1.5 (0.9,2.5)	0.6 (0.3,1.1)	1.1 (0.1,9.2)	0.2 (0.0,85.5)	*NA*	*NA*	2.9 (1.0,9.0)	1.5 (0.5,5.1)	0.9 (0.4,2.1)	0.5 (0.2,1.5)
1980-1989	2.9 (1.9,4.4)	0.6 (0.4,1.0)	2.0 (1.1,3.6)	0.5 (0.2,0.9)	3.6 (0.4,29.6)	0.4 (0.0,15.5)	*NA*	*NA*	2.1 (0.6,7.7)	0.7 (0.2,3.0)	1.5 (0.6,3.4)	0.6 (0.2,1.6)
1990-2006	2.4 (1.5,4.1)	0.3 (0.2,0.5)	0.5 (0.1,2.0)	0.0 (0.0,0.3)	21.3 (4.4,102.4)	0.8 (0.0,18.5)	*NA*	*NA*	0.7 (0.1,5.8)	0.1 (0.0,1.7)	2.4 (1.1,5.1)	0.7 (0.3,1.8)
*P*trend	<0.0001	<0.0001	0.3187	<0.0001	0.0060	0.5342	<0.0001	0.9769	0.7960	0.0490	0.0257	0.7080
Attained Age												
5-19 years	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
10-19 years	0.9 (0.4,2.0)	1.0 (0.4,2.3)	1.2 (0.3,3.9)	1.1 (0.3,4.2)	*NA*	*NA*	0.8 (0.1,7.4)	0.7 (0.1,6.8)	*NA*	*NA*	1.0 (0.2,4.4)	1.3 (0.2,6.9)
20-29 years	0.6 (0.3,1.4)	0.9 (0.4,2.3)	0.6 (0.2,2.1)	0.9 (0.2,3.4)	0.4 (0.0,4.1)	0.6 (0.1,5.9)	0.6 (0.1,5.1)	1.4 (0.2,11.2)	*NA*	*NA*	0.4 (0.1,2.0)	0.5 (0.1,3.2)
30-39 years	0.6 (0.3,1.4)	1.6 (0.7,3.9)	0.7 (0.2,2.5)	2.3 (0.6,8.5)	0.1 (0.0,1.7)	0.3 (0.0,7.7)	0.1 (0.0,1.2)	0.7 (0.1,7.8)	*NA*	*NA*	0.7 (0.2,3.5)	1.3 (0.2,7.8)
40-49 years	0.4 (0.2,1.0)	2.6 (1.0,6.4)	0.4 (0.1,1.3)	2.1 (0.5,9.0)	0.1 (0.0,0.8)	0.9 (0.0,20.2)	0.0 (0.0,0.5)	0.6 (0.0,13.5)	*NA*	*NA*	0.8 (0.2,4.0)	2.9 (0.5,16.5)
50+ years	0.2 (0.1,0.4)	4.0 (1.4,11.2)	0.4 (0.1,1.3)	6.0 (1.5,24.8)	0.0 (0.0,0.2)	*NA*	*NA*	*NA*	*NA*	*NA*	0.5 (0.1,2.6)	3.9 (0.6,26.3)
*P*trend	<0.0001	0.0001	0.0006	0.0010	0.0020	0.6828	<0.0001	0.6138	0.5042	0.0001	0.3771	0.0666

Table 7.4 Relative risks of the standardized mortality ratio and excess mortality ratios per 10,000 person-years estimated using a univariate model, by potential explanatory factors, for the British Childhood Cancer Survivor Study

Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia, O: observed, E: expected, RR: relative risks, SMR: standardized mortality ratio, EMR: excess mortality ratio, CI: confidence intervals, NA: not possible to reliably calculate due to very small numbers

	All Respiratory		Pneumonia		Chronic Lower Respiratory Disease		Fibrosis		Pneumonitis		Other Respiratory	
	RR: SMR (95%CI)	EMR (95%CI)	RR: SMR (95%CI)	EMR (95%CI)	RR: SMR (95%CI)	EMR (95%CI)	RR: SMR (95%CI)	EMR (95%CI)	RR: SMR (95%CI)	EMR (95%CI)	RR: SMR (95%CI)	EMR (95%CI)
Sex												
Male	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Female	1.1 (0.8,1.5)	0.8 (0.5,1.1)	1.1 (0.7,1.8)	0.7 (0.4,1.2)	2.6 (0.8,9.2)	4.7 (0.5,44.2)	2.1 (0.7,5.9)	1.9 (0.6,5.4)	1.0 (0.4,2.7)	0.7 (0.3,1.8)	0.7 (0.4,1.3)	0.6 (0.3,1.3)
*P*heterogeneity	0.6243	0.1861	0.6489	0.2185	0.1196	0.1201	0.1693	0.2474	0.9454	0.4345	0.2149	0.1596
First Primary Neoplasm Type												
CNS (excluding PNET)	2.2 (1.1,4.1)	2.3 (1.1,4.8)	2.5 (1.0,6.4)	2.6 (0.9,7.5)	0.3 (0.0,2.3)	*NA*	*NA*	*NA*	5.0 (0.7,38.7)	4.9 (0.6,39.3)	1.7 (0.5,5.8)	2.0 (0.4,10.1)
PNET	3.5 (1.6,7.7)	3.8 (1.6,9.0)	5.2 (1.8,15.2)	5.4 (1.7,17.5)	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	2.4 (0.5,11.8)	2.9 (0.4,19.8)
Leukemia (excluding AML)	0.9 (0.4,1.8)	0.8 (0.3,1.9)	1.0 (0.3,3.0)	0.9 (0.3,3.1)	*NA*	*NA*	*NA*	*NA*	0.3 (0.0,4.9)	0.3 (0.0,5.7)	1.1 (0.3,4.3)	1.2 (0.2,6.9)
AML	1.4 (0.4,5.0)	1.4 (0.3,5.7)	*NA*	*NA*	3.7 (0.3,49.0)	1.4 (0.1,17.5)	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
Hodgkin Lymphoma	0.6 (0.2,1.5)	0.5 (0.1,1.7)	0.5 (0.1,2.2)	0.3 (0.0,3.2)	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	0.9 (0.2,4.7)	0.9 (0.1,8.0)
Non-Hodgkin Lymphoma	0.6 (0.2,1.8)	0.5 (0.1,2.1)	0.5 (0.1,2.8)	0.4 (0.0,3.8)	0.7 (0.1,8.0)	*NA*	*NA*	*NA*	*NA*	*NA*	0.4 (0.0,4.2)	0.2 (0.0,58.4)
Neuroblastoma	1.0 (0.3,2.6)	0.9 (0.3,2.8)	0.4 (0.0,3.2)	0.1 (0.0,665145.6)	1.2 (0.1,15.6)	2.0 (0.1,43.0)	*NA*	*NA*	1.5 (0.1,23.9)	1.5 (0.1,26.2)	1.2 (0.2,7.2)	1.3 (0.1,11.2)
Non-Heritable Retinoblastoma	0.1 (0.0,1.0)	0.0 (0.0,163.7)	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	0.6 (0.1,5.5)	0.6 (0.0,10.1)
Heritable Retinoblastoma	0.7 (0.2,2.2)	0.6 (0.1,2.6)	1.0 (0.2,4.5)	1.1 (0.2,5.7)	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	0.7 (0.1,7.5)	0.8 (0.1,12.7)
Wilms	0.6 (0.2,1.5)	0.5 (0.1,1.6)	0.2 (0.0,1.6)	0.1 (0.0,4.8)	0.7 (0.1,8.4)	*NA*	*NA*	*NA*	*NA*	*NA*	1.0 (0.2,5.0)	0.8 (0.1,8.0)
Bone Sarcoma	0.2 (0.0,1.2)	*NA*	*NA*	*NA*	0.7 (0.1,7.6)	0.5 (0.0,6.0)	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
Soft Tissue Sarcoma	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Germ Cell Tumors	1.6 (0.6,3.9)	1.5 (0.5,4.3)	2.3 (0.7,8.0)	2.3 (0.6,8.8)	1.1 (0.1,12.9)	*NA*	*NA*	*NA*	1.9 (0.1,31.1)	1.9 (0.1,32.9)	0.7 (0.1,7.2)	0.8 (0.1,12.6)
Other	0.5 (0.2,1.5)	0.3 (0.1,1.8)	0.2 (0.0,1.9)	*NA*	0.4 (0.0,4.7)	*NA*	*NA*	*NA*	1.3 (0.1,21.1)	1.2 (0.1,22.8)	0.8 (0.1,4.7)	1.0 (0.1,8.5)
*P*heterogeneity	<0.0001	<0.0001	<0.0001	<0.0001	0.5536	0.1888	0.2201	0.2249	0.0016	0.0026	0.5939	0.6510
Age at Diagnosis												
0-4 years	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
5-9 years	0.7 (0.5,1.1)	0.8 (0.5,1.4)	0.8 (0.4,1.5)	1.0 (0.5,2.1)	1.4 (0.2,10.2)	*NA*	0.4 (0.1,1.9)	0.3 (0.1,2.0)	0.4 (0.1,1.3)	0.3 (0.1,1.2)	1.0 (0.4,2.2)	1.1 (0.4,2.6)
10-14 years	0.8 (0.5,1.2)	1.0 (0.6,1.7)	1.0 (0.5,1.8)	1.5 (0.7,3.1)	1.0 (0.1,6.8)	*NA*	1.1 (0.3,4.5)	1.1 (0.3,4.6)	0.4 (0.1,1.3)	0.3 (0.1,1.0)	0.8 (0.3,1.9)	0.8 (0.2,2.4)
*P*trend	0.2738	0.9293	0.9444	0.2539	0.8895	0.4420	0.9640	0.9541	0.1281	0.0628	0.5977	0.6727
Treatment Era												
<1970	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1970-1979	1.5 (1.0,2.3)	1.1 (0.7,1.7)	1.3 (0.7,2.3)	0.8 (0.4,1.5)	0.6 (0.1,5.5)	0.9 (0.1,15.0)	*NA*	*NA*	2.9 (0.7,11.6)	3.8 (1.0,14.5)	0.9 (0.3,2.4)	0.6 (0.2,2.1)
1980-1989	1.7 (1.1,2.9)	0.9 (0.6,1.6)	1.5 (0.8,2.9)	0.6 (0.3,1.3)	1.0 (0.1,10.6)	0.5 (0.0,8.9)	*NA*	*NA*	2.0 (0.3,11.6)	3.8 (0.7,21.1)	1.9 (0.7,5.3)	1.4 (0.4,4.9)
1990-2006	1.2 (0.6,2.2)	0.4 (0.2,0.8)	0.3 (0.1,1.2)	0.1 (0.0,0.3)	3.6 (0.4,31.0)	0.8 (0.1,10.8)	*NA*	*NA*	0.6 (0.0,8.4)	1.5 (0.1,21.0)	3.1 (1.0,9.4)	1.8 (0.5,7.1)
*P*trend	0.2230	0.0153	0.5303	<0.0001	0.3824	0.8376	0.4018	0.4424	0.9683	0.2870	0.0210	0.2873
Attained Age												
5-9 years	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
10-19 years	0.8 (0.4,1.9)	0.9 (0.4,2.2)	1.0 (0.3,3.4)	0.8 (0.2,3.1)	*NA*	*NA*	0.7 (0.1,6.6)	0.8 (0.1,7.5)	*NA*	*NA*	1.1 (0.2,5.0)	1.3 (0.2,7.1)
20-29 years	0.6 (0.3,1.5)	0.7 (0.3,1.8)	0.5 (0.1,1.7)	0.4 (0.1,1.7)	0.5 (0.0,6.6)	*NA*	0.5 (0.1,5.1)	1.2 (0.1,11.1)	*NA*	*NA*	0.6 (0.1,3.2)	0.5 (0.1,3.9)
30-39 years	0.6 (0.3,1.5)	1.1 (0.4,2.8)	0.5 (0.1,1.9)	0.8 (0.2,3.2)	0.2 (0.0,3.9)	*NA*	0.1 (0.0,1.1)	0.5 (0.0,6.7)	*NA*	*NA*	1.4 (0.2,7.7)	2.1 (0.3,15.8)
40-49 years	0.5 (0.2,1.2)	1.6 (0.6,4.3)	0.3 (0.1,1.0)	0.6 (0.1,2.9)	0.1 (0.0,2.2)	*NA*	0.0 (0.0,0.7)	0.5 (0.0,15.6)	*NA*	*NA*	1.9 (0.3,11.6)	5.3 (0.6,43.9)
50+ years	0.2 (0.1,0.6)	2.5 (0.8,7.9)	0.3 (0.1,1.2)	1.2 (0.3,6.2)	0.0 (0.0,0.7)	*NA*	*NA*	*NA*	*NA*	*NA*	1.2 (0.2,8.9)	6.4 (0.6,67.1)
*P*trend	0.0003	0.0127	0.0018	0.5757	0.0742	1.0000	0.0003	0.5474	0.9015	0.0001	0.4031	0.0359

Table 7.5: Relative risks of the standardized mortality ratio and excess mortality ratios per 10,000 person-years estimated using a multivariate model, adjusting for sex, first primary neoplasm type, age at diagnosis, treatment era, and attained age, for the British Childhood Cancer Survivor Study

Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia, O: observed, E: expected, RR: relative risks, SMR: standardized mortality ratio, EMR: excess mortality ratio, CI: confidence intervals, NA: not possible to reliably calculate due to very small numbers

Patient Characteristic	Respiratory Death	%	Other Death	%	Total	%
Overall	1067	3.1	33121	96.9	34188	100.0
Sex						
Male	472	3.9	11614	96.1	12086	100.0
Female	595	2.7	21507	97.3	22102	100.0
First Primary Neoplasm Type						
Breast	135	1.3	10477	98.7	10612	100.0
Testicular	98	4.9	1910	95.1	2008	100.0
Cervix	152	5.7	2492	94.3	2644	100.0
Melanoma	25	1.1	2295	98.9	2320	100.0
Hodgkin Lymphoma	134	4.4	2937	95.6	3071	100.0
CNS (excluding PNET)	129	3.2	3865	96.8	3994	100.0
Non-Hodgkin Lymphoma	72	4.2	1647	95.8	1719	100.0
Thyroid	13	3.1	402	96.9	415	100.0
Gastrointestinal	47	3.4	1346	96.6	1393	100.0
Soft Tissue Sarcoma	30	3.4	863	96.6	893	100.0
Ovary	22	3.1	695	96.9	717	100.0
Bladder	27	4.6	555	95.4	582	100.0
Other Genitourinary	35	4.1	819	95.9	854	100.0
Head & Neck	42	6.1	648	93.9	690	100.0
Leukemia (excluding AML)	25	3.3	743	96.7	768	100.0
Other	26	4.9	501	95.1	527	100.0
Bone Tumor	11	3.0	361	97.0	372	100.0
Acute Myeloid Leukemia	12	5.5	205	94.5	217	100.0
Lung	29	10.1	258	89.9	287	100.0
CNS PNET	3	2.9	102	97.1	105	100.0
Age at Diagnosis						
Mean (SD)	33.2	6	22.1	5.8	33.1	5.8
15-19	53	3.8	1360	96.2	1413	100.0
20-24	80	3.3	2329	96.7	2409	100.0
25-29	136	2.9	4592	97.1	4728	100.0
30-34	256	2.8	8927	97.2	9183	100.0
35-39	542	3.3	15913	96.7	16455	100.0
Treatment Era						
1971-1979	447	4.7	8984	95.3	9431	100.0
1980-1989	412	3.3	11913	96.7	12325	100.0
1990-1990	169	1.9	8812	98.1	8981	100.0
2000-2006	39	1.1	3412	98.9	3451	100.0
Years Follow-Up						
Mean (SD)	21.9	0.0	14.6	0.0	14.8	0.0
5-9 years	159	1.1	14237	98.9	14396	100.0
10-19 years	277	2.6	10509	97.4	10786	100.0
20-29 years	381	6.6	5730	93.8	6111	100.0
30-39 years	240	9.6	2505	91.3	2745	100.0
40+ years	10	7.1	140	93.3	150	100.0
Attained Age						
Mean (SD)	55.2	0.4	47.7	0.1	47.9	0.1
20-29 years	20	1.6	1252	98.4	1272	100.0
30-39 years	103	1.8	5735	98.2	5838	100.0
40-49 years	227	1.5	14424	98.5	14651	100.0
50-59 years	314	4.2	7183	95.8	7497	100.0
60+ years	403	8.2	4527	91.8	4930	100.0

Table 7.6: Study characteristics of the Teenage and Young Adult Cancer Survivor Study (TYACSS)

Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia, SD: standard deviation

		All Respiratory			Pneumonia			Chronic Lower Respiratory Disease		
	Person-Years	O/E	SMR (95%CI)	AER (95%CI)	O/E	SMR (95%CI)	AER (95%CI)	O/E	SMR (95%CI)	AER (95%CI)
Overall	2,867,878	1067/643.2	1.7 (1.6,1.8)	1.5 (1.3,1.7)	390/191.1	2.0 (1.8,2.3)	0.7 (0.6,0.8)	388/295.0	1.3 (1.2,1.5)	0.3 (0.2,0.5)
Sex										
Male	1,096,504	472/265.3	1.8 (1.6,1.9)	1.9 (1.5,2.3)	186/86.2	2.2 (1.9,2.5)	0.9 (0.7,1.2)	144/112.1	1.3 (1.1,1.5)	0.3 (0.1,0.5)
Female	1,771,374	595/378.0	1.6 (1.5,1.7)	1.2 (1.0,1.5)	204/104.9	1.9 (1.7,2.2)	0.6 (0.4,0.7)	244/183.0	1.3 (1.2,1.5)	0.3 (0.2,0.5)
First Primary Neoplasm Type										
Breast	444,041	135/117.8	1.1 (1.0,1.4)	0.4 (-0.1,0.9)	44/32.2	1.4 (1.0,1.8)	0.3 (-0.0,0.6)	56/58.4	1.0 (0.7,1.2)	-0.1 (-0.4,0.3)
Testicular	358,212	98/79.7	1.2 (1.0,1.5)	0.5 (-0.0,1.1)	34/26.5	1.3 (0.9,1.8)	0.2 (-0.1,0.5)	37/32.7	1.1 (0.8,1.6)	0.1 (-0.2,0.5)
Cervix	384,507	152/85.4	1.8 (1.5,2.1)	1.7 (1.1,2.4)	44/23.5	1.9 (1.4,2.5)	0.5 (0.2,0.9)	87/41.6	2.1 (1.7,2.6)	1.2 (0.7,1.7)
Melanoma	295,141	25/57.1	0.4 (0.3,0.6)	-1.1 (-1.4,-0.8)	5/17.1	0.3 (0.1,0.7)	-0.4 (-0.6,-0.3)	13/25.7	0.5 (0.3,0.9)	-0.4 (-0.7,-0.2)
Hodgkin Lymphoma	270,034	134/42.8	3.1 (2.6,3.7)	3.4 (2.5,4.2)	39/14.2	2.7 (2.0,3.8)	0.9 (0.5,1.4)	40/17.4	2.3 (1.6,3.1)	0.8 (0.4,1.3)
CNS (excluding PNET)	227,447	129/41.5	3.1 (2.6,3.7)	3.8 (2.9,4.8)	63/13.0	4.8 (3.7,6.2)	2.2 (1.5,2.9)	18/17.9	1.0 (0.6,1.6)	0.0 (-0.4,0.4)
Non-Hodgkin Lymphoma	124,611	72/26.0	2.8 (2.2,3.5)	3.7 (2.4,5.0)	30/8.2	3.7 (2.5,5.2)	1.8 (0.9,2.6)	15/11.3	1.3 (0.7,2.2)	0.3 (-0.3,0.9)
Thyroid	111,952	13/20.9	0.6 (0.3,1.1)	-0.7 (-1.3,-0.1)	4/6.1	0.7 (0.2,1.7)	-0.2 (-0.5,0.2)	6/9.6	0.6 (0.2,1.4)	-0.3 (-0.7,0.1)
Gastrointestinal	102,795	47/33.4	1.4 (1.0,1.9)	1.3 (0.0,2.6)	17/9.6	1.8 (1.0,2.8)	0.7 (-0.1,1.5)	20/16.0	1.3 (0.8,1.9)	0.4 (-0.5,1.2)
Soft Tissue Sarcoma	92,295	30/20.4	1.5 (1.0,2.1)	1.0 (-0.1,2.2)	13/6.1	2.1 (1.1,3.6)	0.7 (-0.0,1.5)	13/9.2	1.4 (0.8,2.4)	0.4 (-0.4,1.2)
Ovary	80,825	22/18.1	1.2 (0.8,1.8)	0.5 (-0.6,1.6)	12/5.0	2.4 (1.2,4.2)	0.9 (0.0,1.7)	7/8.9	0.8 (0.3,1.6)	-0.2 (-0.9,0.4)
Bladder	83,660	27/31.6	0.9 (0.6,1.2)	-0.6 (-1.8,0.7)	9/9.2	1.0 (0.4,1.9)	-0.0 (-0.7,0.7)	14/15.0	0.9 (0.5,1.6)	-0.1 (-1.0,0.8)
Other Genitourinary	68,726	35/21.3	1.6 (1.1,2.3)	2.0 (0.3,3.7)	13/6.0	2.2 (1.2,3.7)	1.0 (-0.0,2.0)	14/10.4	1.3 (0.7,2.3)	0.5 (-0.5,1.6)
Head & Neck	57,915	42/16.4	2.6 (1.9,3.5)	4.4 (2.2,6.6)	17/4.8	3.5 (2.0,5.6)	2.1 (0.7,3.5)	16/7.6	2.1 (1.2,3.4)	1.5 (0.1,2.8)
Leukemia (excluding AML)	39,610	25/5.2	4.8 (3.1,7.1)	5.0 (2.5,7.5)	9/1.8	5.1 (2.3,9.6)	1.8 (0.3,3.3)	6/2.0	3.0 (1.1,6.6)	1.0 (-0.2,2.2)
Other	48,857	26/11.5	2.3 (1.5,3.3)	3.0 (0.9,5.0)	14/3.4	4.1 (2.3,6.9)	2.2 (0.7,3.7)	8/5.3	1.5 (0.6,2.9)	0.5 (-0.6,1.7)
Bone Tumor	33,461	11/4.6	2.4 (1.2,4.3)	1.9 (-0.0,3.9)	8/1.5	5.2 (2.2,10.2)	1.9 (0.3,3.6)	1/1.8	0.6 (0.0,3.1)	-0.2 (-0.8,0.3)
Acute Myeloid Leukemia	20,536	12/2.1	5.7 (2.9,9.9)	4.8 (1.5,8.1)	3/0.8	4.0 (0.8,11.6)	1.1 (-0.6,2.7)	1/0.7	1.4 (0.0,7.6)	0.1 (-0.8,1.1)
Lung	19,281	29/7.0	4.2 (2.8,6.0)	11.4 (5.9,16.9)	9/2.0	4.5 (2.1,8.5)	3.6 (0.6,6.7)	16/3.3	4.8 (2.7,7.8)	6.6 (2.5,10.6)
CNS PNET	3,973	3/0.4	6.8 (1.4,19.9)	6.4 (-2.1,15.0)	3/0.2	18.7 (3.9,54.7)	7.1 (-1.4,15.7)	0/0.2	0	-0.4 (-0.4,-0.4)
Age at Diagnosis										
15-19 years	192,725	53/8.7	6.1 (4.6,8.0)	2.3 (1.6,3.0)	17/3.8	4.4 (2.6,7.1)	0.7 (0.3,1.1)	9/1.6	5.6 (2.6,10.6)	0.4 (0.1,0.7)
20-24 years	330,513	80/24.5	3.3 (2.6,4.1)	1.7 (1.1,2.2)	31/9.8	3.1 (2.1,4.5)	0.6 (0.3,1.0)	17/6.9	2.5 (1.4,3.9)	0.3 (0.1,0.6)
25-29 years	540,128	136/67.4	2.0 (1.7,2.4)	1.3 (0.8,1.7)	66/23.3	2.8 (2.2,3.6)	0.8 (0.5,1.1)	29/25.3	1.1 (0.8,1.6)	0.1 (-0.1,0.3)
30-34 years	776,141	256/163.2	1.6 (1.4,1.8)	1.2 (0.8,1.6)	102/49.2	2.1 (1.7,2.5)	0.7 (0.4,0.9)	84/73.2	1.1 (0.9,1.4)	0.1 (-0.1,0.4)
35-39 years	1,028,370	542/379.5	1.4 (1.3,1.6)	1.6 (1.1,2.0)	174/104.9	1.7 (1.4,1.9)	0.7 (0.4,0.9)	249/188.0	1.3 (1.2,1.5)	0.6 (0.3,0.9)
Treatment Era										
1970-1979	662,969	447/313.7	1.4 (1.3,1.6)	2.0 (1.4,2.6)	146/84.1	1.7 (1.5,2.0)	0.9 (0.6,1.3)	205/160.9	1.3 (1.1,1.5)	0.7 (0.2,1.1)
1980-1989	1,051,484	412/231.5	1.8 (1.6,2.0)	1.7 (1.3,2.1)	157/70.2	2.2 (1.9,2.6)	0.8 (0.6,1.1)	146/105.4	1.4 (1.2,1.6)	0.4 (0.2,0.6)
1990-1999	849,407	169/81.6	2.1 (1.8,2.4)	1.0 (0.7,1.3)	68/30.1	2.3 (1.8,2.9)	0.4 (0.3,0.6)	33/25.4	1.3 (0.9,1.8)	0.1 (-0.0,0.2)
2000-2006	304,018	39/16.4	2.4 (1.7,3.2)	0.7 (0.3,1.1)	19/6.7	2.8 (1.7,4.4)	0.4 (0.1,0.7)	4/3.3	1.2 (0.3,3.1)	0.0 (-0.1,0.2)
Years Follow-Up										
5-9 years	927,451	159/52.6	3.0 (2.6,3.5)	1.1 (0.9,1.4)	86/24.4	3.5 (2.8,4.3)	0.7 (0.5,0.9)	18/9.0	2.0 (1.2,3.2)	0.1 (0.0,0.2)
10-19 years	1,213,840	277/151.9	1.8 (1.6,2.1)	1.0 (0.8,1.3)	121/57.7	2.1 (1.7,2.5)	0.5 (0.3,0.7)	73/50.4	1.4 (1.1,1.8)	0.2 (0.0,0.3)
20-29 years	566,854	381/235.4	1.6 (1.5,1.8)	2.6 (1.9,3.2)	114/63.9	1.8 (1.5,2.1)	0.9 (0.5,1.3)	162/120.6	1.3 (1.1,1.6)	0.7 (0.3,1.2)
30-39 years	154,612	241/188.6	1.3 (1.1,1.4)	3.4 (1.4,5.4)	67/41.5	1.6 (1.3,2.0)	1.6 (0.6,2.7)	130/107.2	1.2 (1.0,1.4)	1.5 (0.0,2.9)
40+ years	5,122	9/14.7	0.6 (0.3,1.2)	-11.0 (-22.5,0.4)	2/3.6	0.6 (0.1,2.0)	-3.1 (-8.5,2.3)	5/7.8	0.6 (0.2,1.5)	-5.5 (-14.0,3.1)
Attained Age										
20-29 years	125,623	20/2.5	7.9 (4.8,12.2)	1.4 (0.7,2.1)	8/1.2	6.7 (2.9,13.2)	0.5 (0.1,1.0)	2/0.1	16.2 (2.0,58.7)	0.1 (-0.1,0.4)
30-39 years	584,866	103/21.7	4.7 (3.9,5.8)	1.4 (1.1,1.7)	54/11.5	4.7 (3.5,6.1)	0.7 (0.5,1.0)	7/1.7	4.1 (1.7,8.5)	0.1 (0.0,0.2)
40-49 years	1,197,156	227/101.6	2.2 (2.0,2.5)	1.0 (0.8,1.3)	113/45.4	2.5 (2.1,3.0)	0.6 (0.4,0.7)	38/21.6	1.8 (1.2,2.4)	0.1 (0.0,0.2)
50-59 years	684,634	314/186.6	1.7 (1.5,1.9)	1.9 (1.4,2.4)	112/58.2	1.9 (1.6,2.3)	0.8 (0.5,1.1)	120/82.3	1.5 (1.2,1.7)	0.5 (0.2,0.9)
60-69 years	240,185	305/225.4	1.4 (1.2,1.5)	3.3 (1.9,4.7)	78/50.5	1.5 (1.2,1.9)	1.1 (0.4,1.9)	161/130.7	1.2 (1.0,1.4)	1.3 (0.2,2.3)
70+ years	35,414	98/105.5	0.9 (0.8,1.1)	-2.1 (-7.6,3.4)	25/24.3	1.0 (0.7,1.5)	0.2 (-2.6,3.0)	60/58.6	1.0 (0.8,1.3)	0.4 (-3.9,4.7)

Table 7.7: Standardized mortality ratios and absolute excess risks per 10,000 person-years for all, pneumonia, and chronic lower respiratory mortality, by potential explanatory factors, for the Teenage and Young Adult Cancer Survivor Study

Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia, O: observed, E: expected, SMR: standardized mortality ratio, AER: absolute excess risk, CI: confidence intervals

		Fibrosis			Pneumonitis			Other Respiratory		
	Person-Years	O/E	SMR (95%CI)	AER (95%CI)	O/E	SMR (95%CI)	AER (95%CI)	O/E	SMR (95%CI)	AER (95%CI)
Overall	2,867,878	74/42.7	1.7 (1.4,2.2)	0.1 (0.1,0.2)	48/22.5	2.1 (1.6,2.8)	0.1 (0.0,0.1)	167/91.9	1.8 (1.6,2.1)	0.3 (0.2,0.4)
Sex										
Male	1,096,504	29/20.7	1.4 (0.9,2.0)	0.1 (-0.0,0.2)	28/10.3	2.7 (1.8,3.9)	0.2 (0.1,0.3)	85/36.1	2.4 (1.9,2.9)	0.4 (0.3,0.6)
Female	1,771,374	45/22.0	2.0 (1.5,2.7)	0.1 (0.1,0.2)	20/12.2	1.6 (1.0,2.5)	0.0 (-0.0,0.1)	82/55.8	1.5 (1.2,1.8)	0.1 (0.0,0.2)
First Primary Neoplasm Type										
Breast	444,041	8/7.0	1.2 (0.5,2.3)	0.0 (-0.1,0.1)	4/3.6	1.1 (0.3,2.8)	0.0 (-0.1,0.1)	23/16.6	1.4 (0.9,2.1)	0.1 (-0.1,0.4)
Testicular	358,212	9/6.1	1.5 (0.7,2.8)	0.1 (-0.1,0.2)	3/3.2	0.9 (0.2,2.7)	-0.0 (-0.1,0.1)	15/11.2	1.3 (0.8,2.2)	0.1 (-0.1,0.3)
Cervix	384,507	7/5.0	1.4 (0.6,2.9)	0.1 (-0.1,0.2)	2/2.8	0.7 (0.1,2.6)	-0.0 (-0.1,0.1)	12/12.5	1.0 (0.5,1.7)	-0.0 (-0.2,0.2)
Melanoma	295,141	2/3.7	0.5 (0.1,2.0)	-0.1 (-0.2,0.0)	2/2.1	0.9 (0.1,3.4)	-0.0 (-0.1,0.1)	3/8.5	0.4 (0.1,1.0)	-0.2 (-0.3,-0.1)
Hodgkin Lymphoma	270,034	19/2.8	6.7 (4.0,10.4)	0.6 (0.3,0.9)	3/1.6	1.8 (0.4,5.4)	0.1 (-0.1,0.2)	33/6.7	4.9 (3.4,6.9)	1.0 (0.6,1.4)
CNS (excluding PNET)	227,447	3/2.8	1.1 (0.2,3.2)	0.0 (-0.1,0.2)	19/1.5	12.3 (7.4,19.2)	0.8 (0.4,1.1)	26/6.3	4.2 (2.7,6.1)	0.9 (0.4,1.3)
Non-Hodgkin Lymphoma	124,611	4/1.8	2.2 (0.6,5.5)	0.2 (-0.1,0.5)	3/1.0	3.1 (0.6,9.0)	0.2 (-0.1,0.4)	20/3.7	5.3 (3.3,8.2)	1.3 (0.6,2.0)
Thyroid	111,952	0/1.3	0	-0.1 (-0.1,-0.1)	0/0.7	0	-0.1 (-0.1,-0.1)	3/3.1	1.0 (0.2,2.8)	-0.0 (-0.3,0.3)
Gastrointestinal	102,795	3/2.4	1.2 (0.3,3.6)	0.1 (-0.3,0.4)	0/1.1	0	-0.1 (-0.1,-0.1)	7/4.3	1.6 (0.7,3.4)	0.3 (-0.2,0.8)
Soft Tissue Sarcoma	92,295	1/1.4	0.7 (0.0,4.0)	-0.0 (-0.3,0.2)	1/0.7	1.4 (0.0,7.7)	0.0 (-0.2,0.2)	2/2.9	0.7 (0.1,2.5)	-0.1 (-0.4,0.2)
Ovary	80,825	0/1.1	0	-0.1 (-0.1,-0.1)	0/0.6	0	-0.1 (-0.1,-0.1)	3/2.6	1.2 (0.2,3.4)	0.0 (-0.4,0.5)
Bladder	83,660	3/2.6	1.2 (0.2,3.4)	0.1 (-0.4,0.5)	0/1.1	0	-0.1 (-0.1,-0.1)	1/3.8	0.3 (0.0,1.5)	-0.3 (-0.6,-0.1)
Other Genitourinary	68,726	4/1.4	2.8 (0.8,7.1)	0.4 (-0.2,0.9)	1/0.7	1.5 (0.0,8.1)	0.0 (-0.2,0.3)	3/2.8	1.1 (0.2,3.1)	0.0 (-0.5,0.5)
Head & Neck	57,915	1/1.2	0.8 (0.0,4.5)	-0.0 (-0.4,0.3)	5/0.6	8.8 (2.9,20.6)	0.8 (0.0,1.5)	3/2.1	1.4 (0.3,4.1)	0.1 (-0.4,0.7)
Leukemia (excluding AML)	39,610	4/0.3	12.1 (3.3,31.0)	0.9 (-0.1,1.9)	3/0.2	13.7 (2.8,39.9)	0.7 (-0.2,1.6)	3/0.9	3.4 (0.7,10.0)	0.5 (-0.3,1.4)
Other	48,857	1/0.8	1.2 (0.0,6.9)	0.0 (-0.4,0.4)	1/0.4	2.5 (0.1,14.0)	0.1 (-0.3,0.5)	2/1.6	1.2 (0.2,4.5)	0.1 (-0.5,0.6)
Bone Tumor	33,461	1/0.3	3.3 (0.1,18.3)	0.2 (-0.4,0.8)	1/0.2	5.4 (0.1,30.0)	0.2 (-0.3,0.8)	0/0.8	0	-0.2 (-0.2,-0.2)
Acute Myeloid Leukemia	20,536	3/0.1	24.1 (5.0,70.6)	1.4 (-0.3,3.1)	0/0.1	0	-0.0 (-0.0,-0.0)	5/0.4	12.6 (4.1,29.3)	2.2 (0.1,4.4)
Lung	19,281	1/0.5	1.8 (0.0,10.2)	0.2 (-0.8,1.3)	0/0.2	0	-0.1 (-0.1,-0.1)	3/0.9	3.5 (0.7,10.1)	1.1 (-0.7,2.9)
CNS PNET	3,973	0/0.0	0	-0.1 (-0.1,-0.1)	0/0.0	0	-0.0 (-0.0,-0.0)	0/0.1	0	-0.2 (-0.2,-0.2)
Age at Diagnosis										
15-19 years	192,725	8/0.4	21.5 (9.3,42.3)	0.4 (0.1,0.7)	4/0.5	8.4 (2.3,21.4)	0.2 (-0.0,0.4)	15/2.4	6.3 (3.5,10.4)	0.7 (0.3,1.0)
20-24 years	330,513	9/1.3	7.1 (3.2,13.4)	0.2 (0.1,0.4)	7/1.2	5.9 (2.4,12.1)	0.2 (0.0,0.3)	16/5.3	3.0 (1.7,4.9)	0.3 (0.1,0.6)
25-29 years	540,128	7/4.0	1.7 (0.7,3.6)	0.1 (-0.0,0.2)	8/2.8	2.8 (1.2,5.5)	0.1 (-0.0,0.2)	26/11.8	2.2 (1.4,3.2)	0.3 (0.1,0.4)
30-34 years	776,141	21/10.8	1.9 (1.2,3.0)	0.1 (0.0,0.2)	10/6.0	1.7 (0.8,3.1)	0.1 (-0.0,0.1)	39/24.0	1.6 (1.2,2.2)	0.2 (0.0,0.4)
35-39 years	1,028,370	29/26.2	1.1 (0.7,1.6)	0.0 (-0.1,0.1)	19/12.0	1.6 (1.0,2.5)	0.1 (-0.0,0.2)	71/48.3	1.5 (1.1,1.9)	0.2 (0.1,0.4)
Treatment Era										
1970-1979	662,969	28/22.5	1.2 (0.8,1.8)	0.1 (-0.1,0.2)	22/8.6	2.6 (1.6,3.9)	0.2 (0.1,0.3)	46/37.6	1.2 (0.9,1.6)	0.1 (-0.1,0.3)
1980-1989	1,051,484	27/14.7	1.8 (1.2,2.7)	0.1 (0.0,0.2)	14/8.2	1.7 (0.9,2.9)	0.1 (-0.0,0.1)	68/33.1	2.1 (1.6,2.6)	0.3 (0.2,0.5)
1990-1999	849,407	17/4.7	3.6 (2.1,5.8)	0.1 (0.0,0.2)	9/4.5	2.0 (0.9,3.8)	0.1 (-0.0,0.1)	42/16.9	2.5 (1.8,3.4)	0.3 (0.1,0.4)
2000-2006	304,018	2/0.9	2.3 (0.3,8.5)	0.0 (-0.1,0.1)	3/1.2	2.6 (0.5,7.5)	0.1 (-0.1,0.2)	11/4.3	2.5 (1.3,4.5)	0.2 (0.0,0.4)
Years Follow-Up										
5-9 years	927,451	9/2.0	4.6 (2.1,8.6)	0.1 (0.0,0.1)	8/2.2	3.6 (1.6,7.2)	0.1 (0.0,0.1)	38/15.0	2.5 (1.8,3.5)	0.2 (0.1,0.4)
10-19 years	1,213,840	20/7.5	2.7 (1.6,4.1)	0.1 (0.0,0.2)	8/5.9	1.4 (0.6,2.7)	0.0 (-0.0,0.1)	55/30.4	1.8 (1.4,2.4)	0.2 (0.1,0.3)
20-29 years	566,854	32/15.5	2.1 (1.4,2.9)	0.3 (0.1,0.5)	22/7.7	2.9 (1.8,4.3)	0.3 (0.1,0.4)	51/27.7	1.8 (1.4,2.4)	0.4 (0.2,0.7)
30-39 years	154,612	13/16.3	0.8 (0.4,1.4)	-0.2 (-0.7,0.2)	10/6.2	1.6 (0.8,3.0)	0.2 (-0.2,0.6)	21/17.4	1.2 (0.7,1.8)	0.2 (-0.3,0.8)
40+ years	5,122	0/1.4	0	-2.7 (-2.7,-2.7)	0/0.5	0	-1.0 (-1.0,-1.0)	2/1.3	1.5 (0.2,5.4)	1.3 (-4.1,6.7)
Attained Age										
20-29 years	125,623	2/0.1	39.2 (4.7,141.5)	0.2 (-0.1,0.4)	1/0.1	8.1 (0.2,45.3)	0.1 (-0.1,0.2)	7/1.0	6.7 (2.7,13.8)	0.5 (0.1,0.9)
30-39 years	584,866	14/0.6	22.4 (12.3,37.6)	0.2 (0.1,0.4)	7/1.0	6.8 (2.7,14.1)	0.1 (0.0,0.2)	21/6.8	3.1 (1.9,4.7)	0.2 (0.1,0.4)
40-49 years	1,197,156	13/4.4	2.9 (1.6,5.0)	0.1 (0.0,0.1)	12/4.5	2.7 (1.4,4.7)	0.1 (0.0,0.1)	51/25.7	2.0 (1.5,2.6)	0.2 (0.1,0.3)
50-59 years	684,634	23/10.9	2.1 (1.3,3.2)	0.2 (0.0,0.3)	9/6.9	1.3 (0.6,2.5)	0.0 (-0.1,0.1)	50/28.3	1.8 (1.3,2.3)	0.3 (0.1,0.5)
60-69 years	240,185	16/17.0	0.9 (0.5,1.5)	-0.0 (-0.4,0.3)	16/6.7	2.4 (1.4,3.9)	0.4 (0.1,0.7)	34/20.5	1.7 (1.2,2.3)	0.6 (0.1,1.0)
70+ years	35,414	6/9.6	0.6 (0.2,1.4)	-1.0 (-2.4,0.3)	3/3.4	0.9 (0.2,2.6)	-0.1 (-1.1,0.9)	4/9.6	0.4 (0.1,1.1)	-1.6 (-2.7,-0.5)

Table 7.7 (*continued*): Standardized mortality ratios and absolute excess risks per 10,000 person-years for fibrosis, pneumonitis, and other respiratory mortality, by potential explanatory factors, for the Teenage and Young Adult Cancer Survivor Study

Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia, O: observed, E: expected, SMR: standardized mortality ratio, AER: absolute excess risk, CI: confidence intervals

	All Respiratory		Pneumonia		Chronic Lower Respiratory Disease		Fibrosis		Pneumonitis		Other Respiratory	
	RR: SMR (95%CI)	EMR (95%CI)	RR: SMR (95%CI)	EMR (95%CI)	RR: SMR (95%CI)	EMR (95%CI)	RR: SMR (95%CI)	EMR (95%CI)	RR: SMR (95%CI)	EMR (95%CI)	RR: SMR (95%CI)	EMR (95%CI)
Sex												
Male	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Female	1.1 (1.0,1.3)	0.8 (0.6,1.0)	1.1 (0.9,1.5)	0.6 (0.4,0.9)	1.2 (0.9,1.6)	0.8 (0.4,1.5)	2.7 (1.5,4.9)	3.3 (1.4,8.2)	0.8	0.5 (0.2,1.3)	0.8 (0.5,1.2)	0.7 (0.4,1.2)
*P*heterogeneity	0.1452	0.0457	0.2903	0.0121	0.2830	0.4700	0.0006	0.0032	0.5950	0.1499	0.2592	0.1455
First Primary Neoplasm Type												
Breast	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Testicular	1.0 (0.8,1.4)	0.6 (0.2,2.7)	0.9 (0.5,1.5)	0.2 (0.0,4.3)	1.4 (0.8,2.3)	*NA*	2.8 (0.9,8.9)	*NA*	0.6	0.2 (0.0,91528.9)	0.7 (0.3,1.4)	0.5 (0.1,5.2)
Cervix	1.5 (1.2,1.9)	2.3 (1.0,5.5)	1.2 (0.8,1.9)	1.3 (0.5,3.3)	2.2 (1.6,3.1)	*NA*	1.1 (0.4,3.0)	0.9 (0.0,31.3)	0.6	1.0 (0.0,56.0)	0.7 (0.3,1.3)	*NA*
Melanoma	0.4 (0.2,0.6)	*NA*	0.2 (0.1,0.5)	*NA*	0.6 (0.3,1.0)	*NA*	0.5 (0.1,2.4)	1.2 (0.0,44.4)	0.7	*NA*	0.2 (0.1,0.7)	*NA*
Hodgkin Lymphoma	2.3 (1.7,3.0)	6.5 (2.9,14.5)	1.7 (1.1,2.7)	2.3 (0.9,5.8)	2.4 (1.5,3.8)	*NA*	6.2 (2.5,15.7)	20.5 (1.0,415.4)	0.9	0.7 (0.0,110.5)	2.5 (1.3,4.6)	5.9 (1.4,24.5)
CNS (excluding PNET)	2.4 (1.9,3.2)	7.5 (3.4,16.4)	3.2 (2.1,4.8)	5.5 (2.4,12.3)	1.1 (0.6,1.9)	*NA*	1.1 (0.3,4.1)	2.7 (0.1,72.5)	7.8	21.0 (0.7,599.8)	2.2 (1.2,4.1)	5.2 (1.3,21.1)
Non-Hodgkin Lymphoma	2.3 (1.7,3.1)	6.7 (2.9,15.5)	2.5 (1.5,4.2)	4.4 (1.8,10.5)	1.5 (0.8,2.7)	*NA*	2.8 (0.8,9.7)	5.4 (0.2,174.9)	2.0	3.5 (0.1,172.6)	2.9 (1.5,5.6)	6.6 (1.5,27.9)
Thyroid	0.5 (0.3,0.9)	*NA*	0.4 (0.2,1.2)	*NA*	0.7 (0.3,1.6)	*NA*	*NA*	*NA*	*NA*	*NA*	0.6 (0.2,1.9)	0.3 (0.0,225.8)
Gastrointestinal	1.3 (0.9,1.8)	2.0 (0.6,6.2)	1.4 (0.8,2.5)	1.1 (0.3,4.8)	1.4 (0.8,2.4)	*NA*	1.8 (0.5,7.0)	*NA*	*NA*	*NA*	1.1 (0.4,2.6)	1.8 (0.3,12.4)
Soft Tissue Sarcoma	1.2 (0.8,1.8)	2.0 (0.6,6.4)	1.5 (0.8,2.8)	2.2 (0.7,6.7)	1.5 (0.8,2.9)	*NA*	0.8 (0.1,6.5)	3.3 (0.1,120.3)	0.9	*NA*	0.4 (0.1,1.7)	*NA*
Ovary	1.0 (0.6,1.6)	1.8 (0.5,6.4)	1.7 (0.9,3.1)	2.5 (0.8,8.2)	0.8 (0.4,1.8)	*NA*	*NA*	*NA*	*NA*	*NA*	0.8 (0.2,2.6)	0.6 (0.0,78.2)
Bladder	0.8 (0.5,1.3)	*NA*	0.8 (0.4,1.7)	*NA*	1.1 (0.6,2.1)	*NA*	2.3 (0.6,9.4)	8.3 (0.2,280.8)	*NA*	*NA*	0.2 (0.0,1.3)	*NA*
Other Genitourinary	1.5 (1.0,2.2)	3.7 (1.4,10.0)	1.6 (0.9,3.1)	2.4 (0.8,7.6)	1.5 (0.8,2.7)	*NA*	3.4 (1.0,11.5)	8.4 (0.3,268.3)	1.2	*NA*	0.7 (0.2,2.4)	*NA*
Head & Neck	2.3 (1.6,3.3)	7.2 (2.9,17.6)	2.6 (1.5,4.7)	4.3 (1.6,11.8)	2.5 (1.4,4.4)	*NA*	1.2 (0.2,10.1)	*NA*	6.1	14.8 (0.4,518.6)	0.8 (0.2,2.9)	1.0 (0.0,29.5)
Leukemia (excluding AML)	3.3 (2.1,5.1)	10.3 (4.1,25.5)	3.1 (1.5,6.5)	5.2 (1.7,15.9)	3.0 (1.3,7.1)	*NA*	9.6 (2.7,34.1)	32.3 (1.4,757.6)	7.5	19.7 (0.6,700.8)	1.5 (0.4,5.4)	3.2 (0.4,23.7)
Other	1.9 (1.3,2.9)	5.2 (1.9,14.3)	2.9 (1.6,5.4)	5.0 (1.8,14.2)	1.6 (0.8,3.5)	*NA*	1.4 (0.2,11.2)	5.0 (0.1,212.3)	1.6	2.8 (0.0,330.1)	0.8 (0.2,3.3)	0.7 (0.0,116.0)
Bone Tumor	1.6 (0.9,3.0)	3.5 (1.0,12.2)	3.1 (1.4,6.9)	5.7 (1.9,17.7)	0.5 (0.1,3.9)	*NA*	2.7 (0.3,22.5)	*NA*	2.6	5.6 (0.1,372.9)	*NA*	*NA*
Acute Myeloid Leukemia	3.7 (2.0,6.7)	11.0 (4.0,30.1)	2.2 (0.7,7.3)	3.5 (0.7,17.1)	1.4 (0.2,10.0)	*NA*	14.9 (3.8,59.4)	37.0 (1.4,976.2)	*NA*	*NA*	5.4 (2.0,14.9)	12.8 (2.5,64.1)
Lung	4.0 (2.6,6.0)	15.3 (6.2,37.7)	3.6 (1.7,7.5)	6.5 (2.0,21.0)	5.6 (3.1,10.2)	*NA*	3.3 (0.4,26.9)	17.7 (0.4,733.0)	*NA*	*NA*	2.3 (0.7,7.9)	4.0 (0.4,41.3)
CNS PNET	4.3 (1.4,13.6)	14.2 (3.2,62.7)	10.5 (3.2,34.8)	20.8 (5.0,86.3)	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
*P*heterogeneity	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Age at Diagnosis												
15-19 years	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
20-24 years	0.8 (0.5,1.1)	1.0 (0.6,1.6)	1.1 (0.6,2.0)	1.7 (0.7,3.9)	0.6 (0.3,1.3)	0.7 (0.2,2.1)	0.6 (0.2,1.7)	0.7 (0.3,2.0)	1.2	1.2 (0.3,6.0)	0.6 (0.3,1.2)	0.6 (0.2,1.5)
25-29 years	0.6 (0.4,0.9)	0.8 (0.5,1.3)	1.3 (0.7,2.4)	2.2 (0.9,5.2)	0.3 (0.1,0.7)	0.1 (0.0,1.3)	0.3 (0.1,0.9)	0.3 (0.1,1.2)	0.8	0.8 (0.1,4.0)	0.5 (0.2,1.1)	0.5 (0.2,1.3)
30-34 years	0.6 (0.4,0.9)	0.9 (0.5,1.5)	1.2 (0.7,2.3)	2.5 (1.0,6.1)	0.4 (0.2,0.8)	0.3 (0.1,1.1)	0.6 (0.2,1.6)	0.6 (0.2,2.2)	0.6	0.4 (0.1,2.5)	0.4 (0.2,0.9)	0.4 (0.2,1.3)
35-39 years	0.7 (0.5,1.0)	1.2 (0.7,2.0)	1.2 (0.6,2.2)	2.9 (1.2,7.2)	0.5 (0.2,1.0)	0.9 (0.3,2.7)	0.5 (0.2,1.4)	0.3 (0.1,1.4)	0.8	0.4 (0.1,2.1)	0.4 (0.2,0.9)	0.5 (0.2,1.3)
*P*trend	0.2554	0.3826	0.8123	0.0144	0.5776	0.2869	0.3906	0.1296	0.5533	0.0984	0.0571	0.2331
Treatment Era												
1971-1979	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1980-1989	1.0 (0.9,1.2)	1.0 (0.7,1.3)	1.0 (0.8,1.3)	1.1 (0.7,1.7)	0.9 (0.7,1.2)	0.6 (0.3,1.0)	0.9 (0.5,1.7)	1.0 (0.4,2.5)	0.5	0.5 (0.2,1.4)	1.5 (1.0,2.2)	2.1 (0.9,4.8)
1990-1999	1.0 (0.8,1.2)	0.8 (0.6,1.1)	0.9 (0.6,1.2)	0.6 (0.4,1.0)	0.8 (0.5,1.1)	0.4 (0.2,0.9)	1.0 (0.5,2.0)	1.4 (0.5,3.8)	0.4	0.8 (0.2,2.6)	1.9 (1.1,3.0)	2.4 (0.9,6.1)
2000-2006	0.9 (0.7,1.4)	0.6 (0.3,1.0)	1.0 (0.6,1.6)	0.5 (0.2,1.0)	0.6 (0.2,1.6)	0.1 (0.0,5.4)	0.4 (0.1,2.0)	0.4 (0.0,3.8)	0.4	0.9 (0.1,5.2)	1.9 (0.9,4.1)	2.4 (0.8,7.9)
*P*trend	0.7131	0.0258	0.5202	00115	0.1483	0.0040	0.5136	0.9868	0.0767	0.6839	0.0126	0.0933
Attained Age												
20-29 years	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
30-39 years	0.9 (0.5,1.5)	1.4 (0.8,2.5)	0.7 (0.3,1.6)	1.1 (0.4,2.8)	0.5 (0.1,2.4)	1.1 (0.2,7.4)	1.1 (0.2,5.2)	2.9 (0.6,14.1)	1.3	2.7 (0.3,27.6)	0.8 (0.3,2.1)	1.0 (0.4,3.0)
40-49 years	0.5 (0.3,0.8)	1.3 (0.7,2.4)	0.4 (0.2,0.9)	0.8 (0.3,2.3)	0.2 (0.0,1.0)	2.2 (0.4,12.8)	0.2 (0.0,1.0)	1.7 (0.3,9.9)	0.6	3.3 (0.3,38.2)	0.8 (0.3,2.0)	1.6 (0.5,5.0)
50-59 years	0.4 (0.2,0.6)	2.2 (1.1,4.2)	0.3 (0.1,0.7)	1.0 (0.4,3.0)	0.2 (0.0,0.8)	8.6 (1.5,49.5)	0.1 (0.0,0.7)	4.6 (0.7,28.9)	0.3	4.6 (0.3,61.4)	0.9 (0.3,2.3)	3.4 (1.0,12.3)
60-69 years	0.3 (0.2,0.5)	3.8 (1.8,8.0)	0.2 (0.1,0.6)	1.5 (0.5,4.6)	0.1 (0.0,0.6)	11.9 (1.8,76.6)	0.1 (0.0,0.4)	2.4 (0.1,51.9)	0.5	27.6 (2.0,388.4)	1.0 (0.3,2.9)	6.2 (1.3,29.2)
70+ years	0.2 (0.1,0.4)	*NA*	0.2 (0.1,0.4)	0.4 (0.0,58.5)	0.1 (0.0,0.5)	8.2 (0.4,162.8)	0.0 (0.0,0.3)	*NA*	0.1	19.2 (0.3,1157.9)	0.3 (0.1,1.4)	*NA*
*P*trend	<0.0001	0.0002	<0.0001	0.4897	0.0002	<0.0001	<0.0001	0.3456	0.0488	0.3021	0.7295	0.0082

Table 7.8: Relative risks of the standardized mortality ratio and excess mortality ratios per 10,000 person-years estimated using a multivariate model, adjusting for sex, first primary neoplasm type, age at diagnosis, treatment era, and attained age, for the Teenage and Young Adult Cancer Survivor Study

Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia, O: observed, E: expected, RR: relative risks, SMR: standardized mortality ratio, EMR: excess mortality ratio, CI: confidence intervals, NA: not possible to reliably calculate due to very small numbers

	All Respiratory		Pneumonia		Chronic Lower Respiratory Disease		Fibrosis		Pneumonitis		Other Respiratory	
	RR: SMR (95%CI)	**EMR (95%CI)**	**RR: SMR (95%CI)**	**EMR (95%CI)**	**RR: SMR (95%CI)**	**EMR (95%CI)**	**RR: SMR (95%CI)**	**EMR (95%CI)**	**RR: SMR (95%CI)**	**EMR (95%CI)**	**RR: SMR (95%CI)**	**EMR (95%CI)**
Sex												
Male	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Female	0.9 (0.8,1.0)	0.6 (0.5,0.9)	0.9 (0.8,1.1)	0.7 (0.5,0.9)	1.0 (0.8,1.3)	1.2 (0.5,2.9)	1.5 (0.9,2.3)	1.7 (0.4,6.8)	0.6 (0.3,1.1)	0.3 (0.1,1.0)	0.6 (0.5,0.9)	0.3 (0.2,0.7)
*P*heterogeneity	0.0476	0.0055	0.3039	0.0154	0.7236	0.7054	0.1122	0.3973	0.0769	0.0208	0.0024	0.0016
First Primary Neoplasm Type												
Breast	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Testicular	1.1 (0.8,1.4)	1.3 (0.2,7.2)	0.9 (0.6,1.5)	*NA*	1.2 (0.8,1.8)	*NA*	1.3 (0.5,3.3)	*NA*	0.8 (0.2,3.8)	*NA*	1.0 (0.5,1.9)	0.7 (0.1,8.8)
Cervix	1.6 (1.2,2.0)	4.5 (1.1,17.7)	1.4 (0.9,2.1)	*NA*	2.2 (1.6,3.1)	*NA*	1.2 (0.4,3.4)	*NA*	0.7 (0.1,3.6)	*NA*	0.7 (0.3,1.4)	*NA*
Melanoma	0.4 (0.2,0.6)	*NA*	0.2 (0.1,0.5)	*NA*	0.5 (0.3,1.0)	*NA*	0.5 (0.1,2.2)	*NA*	0.9 (0.2,4.7)	*NA*	0.3 (0.1,0.8)	*NA*
Hodgkin Lymphoma	2.7 (2.2,3.5)	8.7 (2.3,33.7)	2.0 (1.3,3.1)	*NA*	2.4 (1.6,3.6)	*NA*	5.8 (2.5,13.2)	*NA*	1.7 (0.4,7.5)	*NA*	3.5 (2.1,6.0)	6.8 (1.5,31.4)
CNS (excluding PNET)	2.7 (2.1,3.5)	10.0 (2.6,38.4)	3.5 (2.4,5.2)	*NA*	1.0 (0.6,1.8)	*NA*	0.9 (0.2,3.5)	*NA*	11.2 (3.8,32.9)	*NA*	3.0 (1.7,5.3)	6.0 (1.3,28.7)
Non-Hodgkin Lymphoma	2.4 (1.8,3.2)	9.5 (2.4,37.8)	2.7 (1.7,4.3)	*NA*	1.4 (0.8,2.5)	*NA*	1.9 (0.6,6.3)	*NA*	2.8 (0.6,12.5)	*NA*	3.9 (2.1,7.0)	9.1 (1.9,43.6)
Thyroid	0.5 (0.3,1.0)	*NA*	0.5 (0.2,1.3)	*NA*	0.7 (0.3,1.5)	*NA*	*NA*	*NA*	*NA*	*NA*	0.7 (0.2,2.3)	*NA*
Gastrointestinal	1.2 (0.9,1.7)	3.4 (0.7,17.9)	1.3 (0.7,2.3)	*NA*	1.3 (0.8,2.2)	*NA*	1.1 (0.3,4.0)	*NA*	*NA*	*NA*	1.2 (0.5,2.8)	1.8 (0.2,20.5)
Soft Tissue Sarcoma	1.3 (0.9,1.9)	2.7 (0.5,15.3)	1.5 (0.8,2.9)	*NA*	1.5 (0.8,2.7)	*NA*	0.6 (0.1,5.0)	*NA*	1.3 (0.1,11.2)	*NA*	0.5 (0.1,2.1)	*NA*
Ovary	1.1 (0.7,1.7)	1.3 (0.1,18.4)	1.8 (0.9,3.3)	*NA*	0.8 (0.4,1.8)	*NA*	*NA*	*NA*	*NA*	*NA*	0.8 (0.2,2.8)	0.3 (0.0,2167.8)
Bladder	0.7 (0.5,1.1)	*NA*	0.7 (0.4,1.5)	*NA*	1.0 (0.5,1.7)	*NA*	1.0 (0.3,3.9)	*NA*	*NA*	*NA*	0.2 (0.0,1.4)	*NA*
Other Genitourinary	1.4 (1.0,2.1)	5.2 (1.1,24.9)	1.6 (0.9,2.9)	*NA*	1.4 (0.8,2.5)	*NA*	2.4 (0.7,8.0)	*NA*	1.3 (0.1,11.9)	*NA*	0.8 (0.2,2.6)	*NA*
Head & Neck	2.2 (1.6,3.2)	11.5 (2.8,47.2)	2.6 (1.5,4.5)	*NA*	2.2 (1.3,3.8)	*NA*	0.7 (0.1,5.7)	*NA*	8.0 (2.2,29.9)	*NA*	1.0 (0.3,3.4)	1.0 (0.0,71.8)
Leukemia (excluding AML)	4.2 (2.7,6.4)	12.9 (3.1,53.3)	3.7 (1.8,7.6)	*NA*	3.1 (1.4,7.3)	*NA*	10.5 (3.2,34.9)	*NA*	12.4 (2.8,55.5)	*NA*	2.5 (0.7,8.2)	3.7 (0.4,32.8)
Other	2.0 (1.3,3.0)	7.7 (1.7,34.2)	3.0 (1.7,5.5)	*NA*	1.6 (0.7,3.3)	*NA*	1.1 (0.1,8.7)	*NA*	2.3 (0.3,20.5)	*NA*	0.9 (0.2,3.8)	0.6 (0.0,816.8)
Bone Tumor	2.1 (1.1,3.9)	4.9 (0.9,26.3)	3.8 (1.8,8.0)	*NA*	0.6 (0.1,4.2)	*NA*	2.8 (0.4,22.8)	*NA*	4.9 (0.5,43.8)	*NA*	*NA*	*NA*
Acute Myeloid Leukemia	5.0 (2.7,8.9)	12.5 (2.8,55.5)	2.9 (0.9,9.3)	*NA*	1.4 (0.2,10.3)	*NA*	21.0 (5.6,79.1)	*NA*	*NA*	*NA*	9.1 (3.5,23.9)	15.6 (2.7,90.2)
Lung	3.6 (2.4,5.4)	29.5 (7.2,121.1)	3.3 (1.6,6.7)	*NA*	5.0 (2.9,8.7)	*NA*	1.6 (0.2,12.7)	*NA*	*NA*	*NA*	2.5 (0.8,8.3)	7.7 (0.9,67.4)
CNS PNET	6.0 (1.9,18.7)	16.7 (2.6,108.8)	13.7	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
*P*heterogeneity	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Age at Diagnosis												
15-19 years	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
20-24 years	0.5 (0.4,0.8)	0.7 (0.5,1.1)	0.7 (0.4,1.3)	0.9 (0.4,2.1)	0.4 (0.2,1.0)	0.8 (0.3,2.5)	0.3 (0.1,0.9)	0.6 (0.2,1.7)	0.7 (0.2,2.4)	1.0 (0.2,4.0)	0.5 (0.2,1.0)	0.5 (0.2,1.3)
25-29 years	0.3 (0.2,0.5)	0.6 (0.3,0.9)	0.6 (0.4,1.1)	1.2 (0.6,2.4)	0.2 (0.1,0.4)	0.2 (0.0,3.4)	0.1 (0.0,0.2)	0.1 (0.0,0.9)	0.3 (0.1,1.1)	0.5 (0.1,2.5)	0.3 (0.2,0.7)	0.4 (0.2,1.0)
30-34 years	0.3 (0.2,0.3)	0.5 (0.3,0.8)	0.5 (0.3,0.8)	1.0 (0.5,2.0)	0.2 (0.1,0.4)	0.4 (0.1,2.3)	0.1 (0.0,0.2)	0.3 (0.1,1.0)	0.2 (0.1,0.6)	0.3 (0.0,1.9)	0.3 (0.1,0.5)	0.3 (0.1,0.8)
35-39 years	0.2 (0.2,0.3)	0.7 (0.4,1.1)	0.4 (0.2,0.6)	1.0 (0.5,2.0)	0.2 (0.1,0.5)	1.5 (0.6,4.0)	0.1 (0.0,0.1)	0.1 (0.0,3.2)	0.2 (0.1,0.6)	0.4 (0.1,1.9)	0.2 (0.1,0.4)	0.3 (0.1,0.9)
*P*trend	<0.0001	0.0527	<0.0001	0.9467	0.0482	0.7007	<0.0001	0.0016	0.0005	0.0819	0.0001	0.0169
Treatment Era												
1971-1979	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
1980-1989	1.2 (1.1,1.4)	0.9 (0.6,1.2)	1.3 (1.0,1.6)	0.9 (0.5,1.4)	1.1 (0.9,1.3)	0.6 (0.2,1.4)	1.5 (0.9,2.5)	1.4 (0.2,11.2)	0.7 (0.3,1.3)	0.3 (0.1,1.2)	1.0 (1.0,1.0)	1.0 (1.0,1.0)
1990-1999	1.5 (1.2,1.7)	0.5 (0.3,0.8)	1.3 (1.0,1.7)	0.5 (0.3,0.8)	1.0 (0.7,1.5)	0.1 (0.0,0.7)	2.9 (1.6,5.3)	1.8 (0.2,13.0)	0.8 (0.4,1.7)	0.3 (0.1,1.1)	1.7 (1.2,2.4)	2.6 (0.5,13.4)
2000-2006	1.7 (1.2,2.3)	0.4 (0.2,0.7)	1.6 (1.0,2.6)	0.4 (0.2,1.0)	0.9 (0.3,2.5)	0.0 (0.0,13.5)	1.9 (0.4,7.9)	0.5 (0.0,9.8)	1.0 (0.3,3.3)	0.3 (0.0,2.2)	2.0 (1.3,3.1)	2.3 (0.4,12.1)
*P*trend	<0.0001	<0.0001	0.0103	0.0020	0.6922	0.0003	0.0023	0.7621	0.5919	0.0619	0.0006	0.7202
Attained Age												
20-29 years	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
30-39 years	0.6 (0.4,1.0)	1.0 (0.6,1.7)	0.7 (0.3,1.5)	1.3 (0.6,3.2)	0.3 (0.1,1.2)	0.6 (0.1,3.6)	0.6 (0.1,2.5)	1.5 (0.3,6.8)	0.8 (0.1,6.8)	1.5 (0.1,16.1)	0.5 (0.2,1.1)	0.5 (0.2,1.5)
40-49 years	0.3 (0.2,0.4)	0.8 (0.4,1.3)	0.4 (0.2,0.8)	1.0 (0.4,2.5)	0.1 (0.0,0.4)	0.9 (0.2,4.8)	0.1 (0.0,0.3)	0.5 (0.1,2.4)	0.3 (0.0,2.5)	0.9 (0.1,10.0)	0.3 (0.1,0.7)	0.4 (0.2,1.3)
50-59 years	0.2 (0.1,0.3)	1.3 (0.8,2.4)	0.3 (0.1,0.6)	1.4 (0.6,3.6)	0.1 (0.0,0.4)	3.7 (0.8,17.9)	0.1 (0.0,0.2)	1.1 (0.2,5.8)	0.2 (0.0,1.3)	0.4 (0.0,15.5)	0.3 (0.1,0.6)	0.7 (0.2,2.0)
60-69 years	0.2 (0.1,0.3)	2.4 (1.2,4.6)	0.2 (0.1,0.5)	2.1 (0.8,5.9)	0.1 (0.0,0.3)	8.4 (1.6,45.7)	0.0 (0.0,0.1)	*NA*	0.3 (0.0,2.2)	5.6 (0.5,60.6)	0.2 (0.1,0.6)	1.2 (0.4,4.0)
70+ years	0.1 (0.1,0.2)	*NA*	0.2 (0.1,0.3)	0.4 (0.0,254852.3)	0.1 (0.0,0.3)	2.7 (0.0,119394.2)	0.0 (0.0,0.1)	*NA*	0.1 (0.0,1.1)	*NA*	0.1 (0.0,0.2)	*NA*
*P*trend	<0.0001	0.1077	<0.0001	0.3523	0.0001	0.0024	<0.0001	0.1649	0.0078	0.7659	<0.0001	0.9770

Table 7.9: Relative risks of the standardized mortality ratio and excess mortality ratios per 10,000 person-years estimated using a univariate model, by potential explanatory factors, for the Teenage and Young Adult Cancer Survivor Study

Abbreviations: CNS: central nervous system, PNET: primitive neuroectodermal tumor, AML: acute myeloid leukemia, O: observed, E: expected, RR: relative risks, SMR: standardized mortality ratio, EMR: excess mortality ratio, CI: confidence intervals, NA: not possible to reliably calculate due to very small numbers

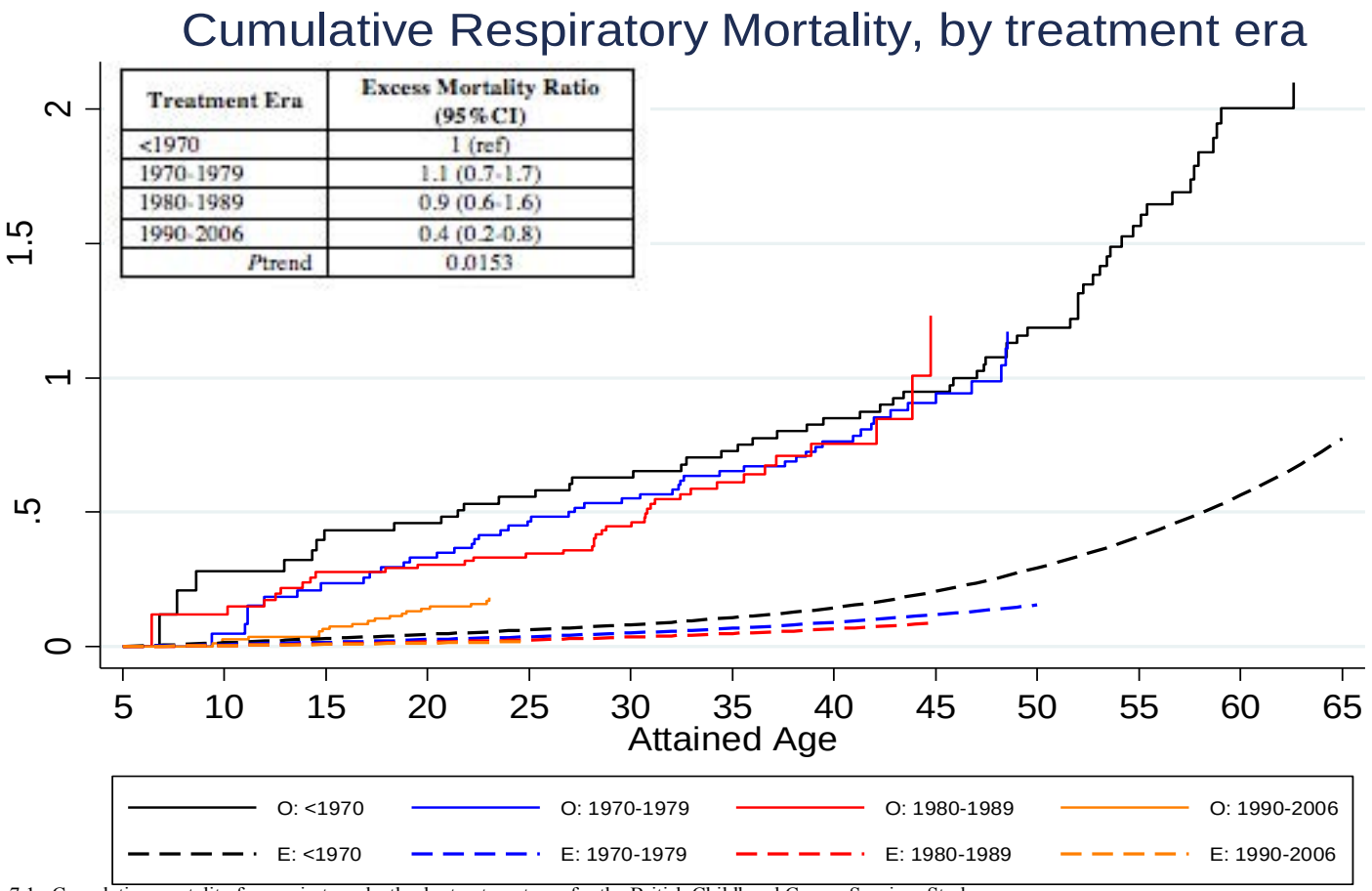

Figure 7.1: Cumulative mortality for respiratory deaths, by treatment era, for the British Childhood Cancer Survivor Study

The table depicts the excess mortality ratio for respiratory deaths, by treatment era, which was calculated in a multivariate Poisson model adjusting for sex, age at diagnosis, first primary neoplasm type, and attained age

Abbreviations: O: observed, E: expected

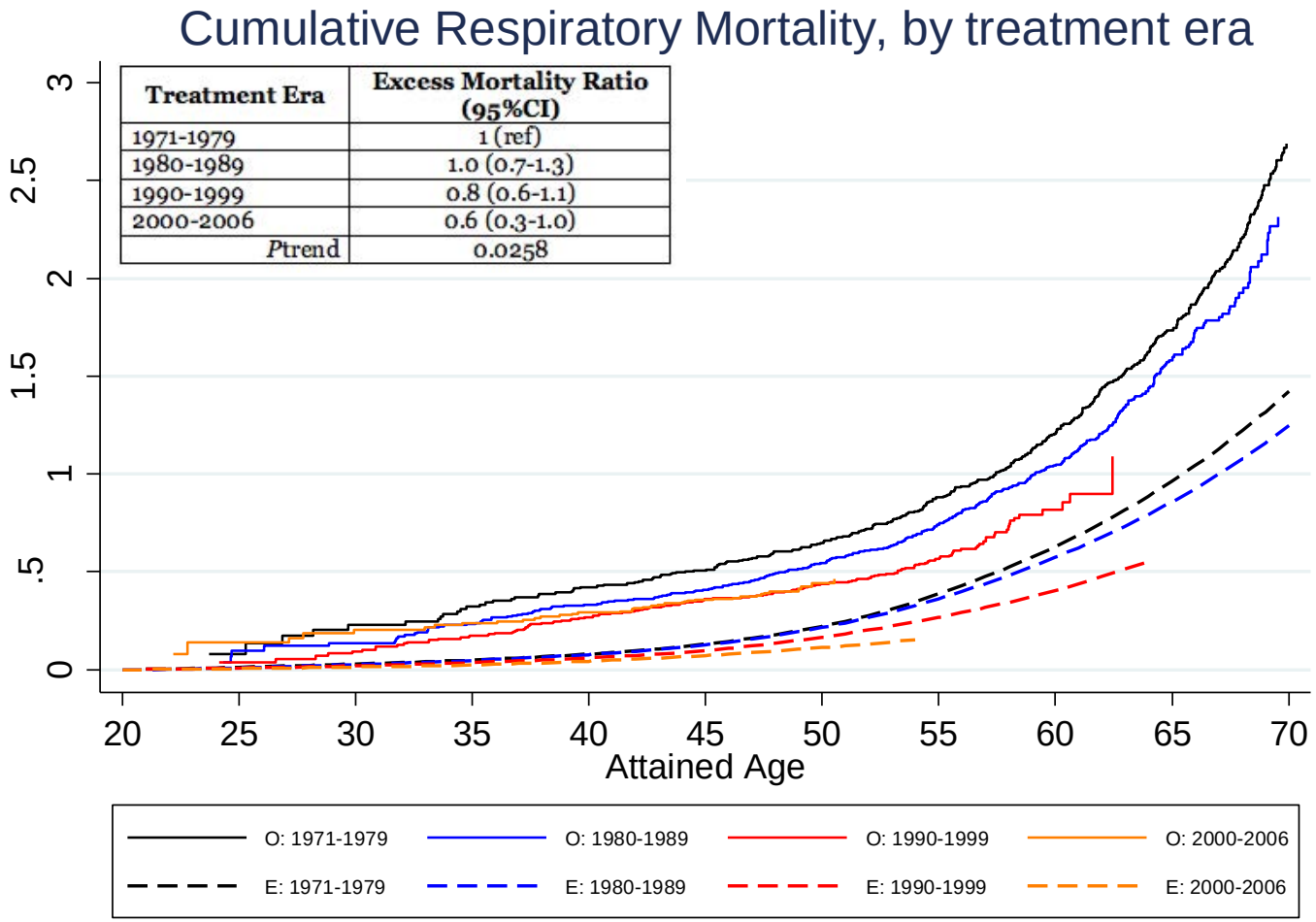

Figure 7.2: Cumulative mortality for respiratory deaths, by treatment era, for the Teenage and Young Adult Cancer Survivor Study
The table depicts the excess mortality ratio for respiratory deaths, by treatment era, which was calculated in a multivariate Poisson model adjusting for sex, age at diagnosis, first primary neoplasm type, and attained age
Abbreviations: O: observed, E: expected

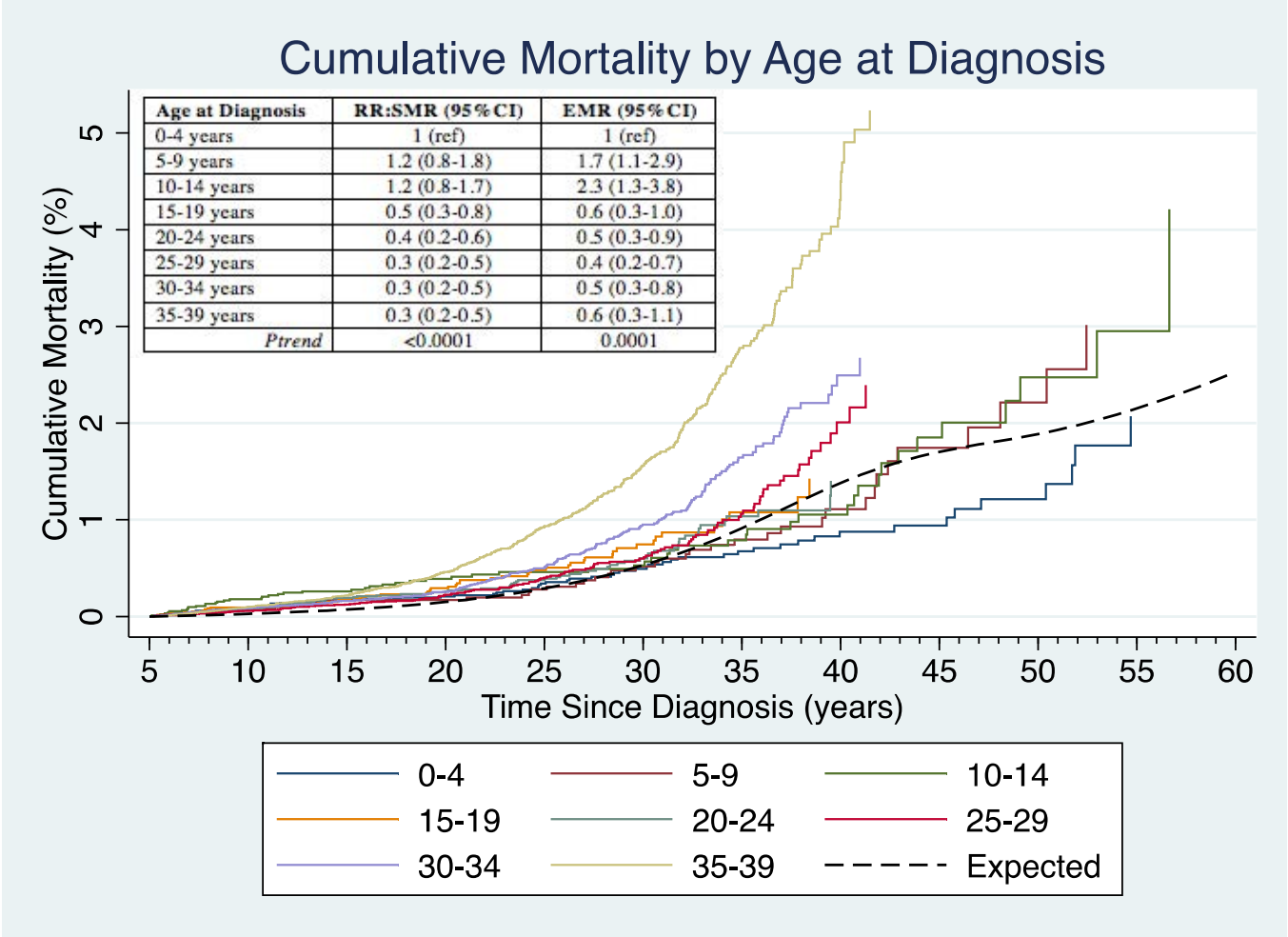

Figure 7.3: Cumulative mortality for respiratory deaths, by age at diagnosis

The table depicts the risk ratio for the SMR and excess mortality ratio for respiratory deaths, by age at diagnosis, which was calculated in a multivariate Poisson model adjusting for sex, first primary neoplasm type, treatment era and attained age

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CHAPTER 8

General Discussion

8.1 Summary

Survival from childhood, teenage, and young adult cancer has improved substantially over recent decades due to improvements in treatment and supportive care, centralization of treatment, and inclusion in clinical trials, with approximately 80% of those diagnosed now surviving at least five years[1,2]. However, improved survival comes at a cost, as certain curative treatments are associated with adverse late effects. With the population of survivors of childhood, teenage, and young adult cancer increasing rapidly with time, it is ever more important to determine adverse late effects in order to improve standards of care for current and future survivors.

Late effects of cancer and its treatment may occur soon after receiving treatment or may not present for many decades[3]. In order to maximize survival whilst also minimizing the risk of long-term sequelae, detailed evidence of the risks faced by survivors is required in order to provide the most appropriate recommendations. Using the BCCSS and TYACSS cohorts, this thesis aimed to add to the current body of literature on late adverse effects subsequent to childhood, teenage, and young adult cancer through the following five studies:

1. Study 1: To assess a wide range of adverse health (mortality, SPNs, hospitalizations/healthcare usage, quality-of-life) and social (educational attainment, marital status, alcohol and smoking habits) outcomes among five-year survivors of childhood bone sarcoma within the BCCSS cohort.
2. Study 2: To assess aspects of mental health dysfunction among five-year survivors of childhood cancer within the BCCSS cohort.
3. Study 3: To quantify the risk of late cause-specific mortality among five-year survivors of childhood cancer within the BCCSS extended cohort.

4. Study 4: To quantify the risk of cardiac mortality among five-year survivors of childhood cancer within the BCCSS extended cohort.
5. Study 5: To quantify the risk of respiratory mortality among five-year survivors of childhood, teenage, and young adult cancers within the BCCSS and TYACSS cohorts.

The findings in this thesis in particular strengthen and expand upon premature mortality among these survivors, providing the most comprehensive studies to date on treatment era effects, very late (beyond 50 years age) mortality, and cause-specific mortality, where cardiac and respiratory deaths were assessed particularly in more detail. Furthermore, this thesis assessed late effects among childhood bone sarcoma survivors, which highlighted the increased risks observed among these survivors for both health and social outcomes. Aspects of mental health dysfunction were also analyzed, with substantial increased risks in dysfunction being observed among survivors of CNS tumors and bone sarcoma. Collectively, these findings provide a unique contribution in the field of late effects of childhood, teenage, and young adult cancers, which will increase knowledge around late effects and have numerous implications on future research in the field.

8.2 Implications of Research

Due to the population-based design, long available follow-up time, and large size of the BCCSS and TYACSS cohorts, the results from the studies included in this thesis provide a reliable and unbiased basis to update, with regards to childhood cancers, and develop, with regards to teenage and young adult cancers, evidence-based clinical follow-up guidelines. Furthermore, these findings will be useful as they provide evidence for risk stratification and planning intervention studies. By contributing to the literature needed to identify future initiatives and form

comprehensive survivorship programs, this thesis has fulfilled its final aim of contributing to the prevention or control of adverse health outcomes among childhood, teenage, and young adult cancer survivors.

8.3 Limitations of Research

The main limitations of the work presented in this thesis relate to the lack of treatment and genetic information, which prevented more detailed interpretation of the results, as well as investigations into the association of adverse health and social outcomes with these risk factors. Although some crude treatment information (i.e. 'yes' or 'no' for radiotherapy, chemotherapy, and surgery) was recorded for the BCCSS and TYACSS cohorts using a population-based method, such as a registry, the vast majority of survivors have missing information. This is a consequence of examining historical cohorts where treatment and genetic data is not easily available, let alone detailed enough to complete analyses that will be useful for risk stratification. Although it would be ideal to retrospectively collect treatment and genetic information for all of the survivors within the two cohorts investigated, it is to date impossible given the high level of costs associated with this task, the lack of interest from funders, and the sheer implausibility for the TYACSS cohort due to it including over 200,000 survivors. For these reasons, treatment and genetic analyses are largely infeasible when using the BCCSS and TYACSS in cohort-approached research, and thus these limitations were unavoidable for this thesis.

These limitations, however, can be overcome within future projects that instead use a case-control approach, making it feasible to collect detailed treatment information and/or genetic material on a proportion of survivors. To date, the BCCSS is currently participating in the

PanCareSurFup (http://www.pancaresurfup.eu//), PROCARDIO (http://www.procardio.eu//), and CEREBRAD (http://www.cerebad-fp7.eu//) projects, which investigate the risk of SPNs, cardiac morbidity and mortality, and cerebrovascular morbidity and mortality through case-control studies. These studies will be able to investigate the dose-response relationship of treatment exposures, whilst also collecting DNA samples – both of which will provide valuable contributions to risk stratification, clinical guidelines, and the current knowledge of late effects after childhood, teenage, and young adult cancers.

8.4 Future Research

Further research is necessary in the field of late effects among childhood, teenage, and young adult cancers. With regards to childhood cancer survivors, additional analyses are needed to determine the very late effects of cancer and its treatment, particularly among individuals who have reached late adulthood and old age. Reassessment of previous literature is also necessary, as treatment of childhood cancer has evolved markedly across decades; thus, findings from more historical cohorts may not be generalizable to individuals more recently diagnosed. Analyses that assess trends in treatment and late effects would also be useful to serve as predictors of the future changes in late effects, which may in return assist in the prevention or control of these adverse outcomes. Finally, more studies assessing dose-response relationships between specific treatments and adverse late effects are needed in order to provide a stronger evidence base for clinical follow-up guidelines.

With regards to teenage and young adult cancer survivors, the Department of Health, National Institute for Health and Clinical Excellence, and National Cancer Research Institute have each

identified a need for accurate information on adverse outcomes among these individuals[4]. Although the findings from this thesis contribute to the knowledge of late effects among individuals diagnosed with cancer between the ages of 15 to 39, further research is needed on mortality, SPNs, chronic health conditions, health related quality-of-life, and many psychosocial outcomes in order to form a body of literature that, when combined, will provide reliable estimates of the risks among teenage and young adult cancer survivors. As a result, additional research will provide a stronger evidence base for counseling and educating survivors, informing clinicians, updating clinical follow-up guidelines, and evaluating current and future treatment protocols.

8.5 Conclusions

The work undertaken in the present thesis aimed to further the current knowledge of late adverse effects of cancer and its treatment among five-year survivors of childhood, teenage, and young adult cancers. The series of studies included in this thesis described a wide range of health and social outcomes, and generally revealed that survivors of cancer diagnosed before the age of 40 years were at an increased risk of each adverse outcome compared to that expected from the general population. Although increased risks were observed, the degree varied by demographic and cancer factors, stressing the importance of providing clinical follow-up that is driven by risk stratification. The findings presented in this thesis add to the literature pertaining to adverse outcomes among childhood, teenage, and young adult cancer survivors and provide a reliable, unbiased, and comprehensive evidence-base for informing survivors and clinicians, updating clinical guidelines, improving follow-up standards, evaluating risks and benefits of future treatment protocol proposals, and health economic evaluations.

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APPENDICES

Appendix 3: Cohort characteristics of the British Childhood Cancer Survivor Study

	Original BCCSS (1940-1991)		Extended BCCSS (1992-2006)		Complete BCCSS (1940-2006)	
	n	%	n	%	N	%
Sex						
Male	9,886	55.0%	9,053	54.8%	18,939	100.0%
Female	8,094	45.0%	7,456	45.2%	15,550	100.0%
First Primary Neoplasm Type						
Central Nervous System Tumor (excluding Primitive Neuroectodermal Tumor)	3,576	19.9%	3,394	20.6%	6,970	100.0%
Central Nervous System Primitive Neuroectodermal Tumor	634	3.5%	564	3.4%	1,198	100.0%
Leukemia (excluding Acute Myeloid Leukemia)	4,516	25.1%	4,977	30.1%	9,493	100.0%
Acute Myeloid Leukemia	336	1.9%	645	3.9%	981	100.0%
Hodgkin Lymphoma	1,326	7.4%	908	5.5%	2,234	100.0%
Non-Hodgkin Lymphoma	878	4.9%	671	4.1%	1,549	100.0%
Neuroblastoma	766	4.3%	769	4.7%	1,535	100.0%
Non-Heritable Retinoblastoma	648	3.6%	358	2.2%	1,006	100.0%
Heritable Retinoblastoma	552	3.1%	198	1.2%	750	100.0%
Wilms	1,441	8.0%	947	5.7%	2,388	100.0%
Bone Sarcoma	664	3.7%	531	3.2%	1,195	100.0%
Soft Tissue Sarcoma	1,181	6.6%	966	5.9%	2,147	100.0%
Other	1,462	8.1%	1,581	9.6%	3,043	100.0%
Age at Diagnosis						
0-4	8,250	45.9%	7,447	45.1%	15,697	100.0%
5-9	4,810	26.8%	4,454	27.0%	9,264	100.0%
10-14	4,920	27.4%	4,608	27.9%	9,528	100.0%
Years Since Diagnosis[a]						
Mean (range)	31.3	(5.0-73.7)	14.0	(5.0-22.2)	23.0	(5.0-73.7)
5-9 years	1,524	8.5%	3,898	23.6%	5,422	100.0%
10-19 years	950	5.3%	10,671	64.6%	11,621	100.0%
20-29 years	5,960	33.1%	1,940	11.8%	7,900	100.0%
30-39 years	5,443	30.3%	0	0.0%	5,443	100.0%
40-49 years	2,806	15.6%	0	0.0%	2,806	100.0%
50-59 years	1,155	6.4%	0	0.0%	1,155	100.0%
60+ years	142	0.8%	0	0.0%	142	100.0%
Attained Age[a]						
Mean (range)	37.8	(5.7-85.6)	20.6	(5.5-36.8)	29.6	(5.5-85.6)
5-9 years	302	1.7%	549	3.3%	851	100.0%
10-19 years	1,404	7.8%	7,041	42.6%	8,445	100.0%
20-29 years	3,057	17.0%	7,676	46.5%	10,733	100.0%
30-39 years	5,375	29.9%	1,243	7.5%	6,618	100.0%
40-49 years	4,850	27.0%	0	0.0%	4,850	100.0%
50-59 years	2,097	11.7%	0	0.0%	2,097	100.0%
60-69 years	813	4.5%	0	0.0%	813	100.0%
70+ years	82	0.5%	0	0.0%	82	100.0%
Radiotherapy						
No	3,878	21.6%	302	1.8%	4,180	100.0%
Yes	9,253	51.5%	97	0.6%	9,350	100.0%
Missing	4,849	27.0%	16,110	97.6%	20,959	100.0%
Chemotherapy						
No	6,065	33.7%	143	0.9%	6,208	100.0%
Yes	6,680	37.2%	252	1.5%	6,932	100.0%
Missing	5,235	29.1%	16,114	97.6%	21,349	100.0%
Surgery						
No	7,477	41.6%	264	1.6%	7,741	100.0%
Yes	6,026	33.5%	150	0.9%	6,176	100.0%
Missing	4,477	24.9%	16,095	97.5%	20,572	100.0%
Vital Status[a]						
Alive	14,300	79.5%	15,706	95.1%	30,006	100.0%
Dead	3,680	20.5%	803	4.9%	4,483	100.0%

[a]As of 28 February 2014

Appendix 4: Cohort characteristics of the Teenage and Young Adult Cancer Survivor Study (TYACSS)

	Complete TYACSS (1971-2006)	
	N	**%**
Sex		
Male	76,666	38.2%
Female	124,279	61.9%
First Primary Neoplasm Type		
Breast	36,236	18.0%
Testicular	24,309	12.1%
Cervix	23,281	11.6%
Melanoma	22,446	11.2%
Hodgkin	16,971	8.5%
CNS (excl. PNET)	16,954	8.4%
NHL	9,467	4.7%
Thyroid	7,809	3.9%
Gastrointestinal	7,224	3.6%
STS	6,130	3.1%
Ovary	4,885	2.4%
Bladder	4,685	2.3%
Other GU	4,672	2.3%
Head & Neck	3,961	2.0%
Leukemia (excl. AML)	3,338	1.7%
Other	3,056	1.5%
Bone Tumor	2,241	1.1%
AML	1,735	0.9%
Lung	1,219	0.6%
PNET	326	0.2%
Age at Diagnosis		
15-19 years	12,249	6.1%
20-24 years	21,257	10.6%
25-29 years	35,894	17.9%
30-34 years	54,541	27.1%
35-39 years	77,004	38.3%
Years Since Diagnosis[a]		
Mean (range)		
5-9 years	38,162	19.0%
10-19 years	77,995	38.8%
20-29 years	53,001	26.4%
30-39 years	28,335	14.1%
40+ years	3,452	1.7%
Attained Age[a]		
Mean (range)		
20-29 years	4,393	2.2%
30-39 years	24,273	12.1%
40-49 years	71,604	35.6%
50-59 years	58,428	29.1%
60-69 years	32,855	16.4%
70-79 years	9,104	4.5%
80+ years	288	0.1%
Vital Status[a]		
Alive	166,757	83.0%
Dead	34,188	17.0%

[a]As of 28 February 2014

Appendix 5: Publication arising from Chapter 3

FULL PAPER

BJC

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Keywords: childhood cancer; bone sarcoma; long-term outcomes; Ewing sarcoma; osteosarcoma; bone cancer; paediatric cancer; late effects

Long-term adverse outcomes in survivors of childhood bone sarcoma: the British Childhood Cancer Survivor Study

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Background: With improved survival, more bone sarcoma survivors are approaching middle age making it crucial to investigate the late effects of their cancer and its treatment. We investigated the long-term risks of adverse outcomes among 5-year bone sarcoma survivors within the British Childhood Cancer Survivor Study.

Methods: Cause-specific mortality and risk of subsequent primary neoplasms (SPNs) were investigated for 664 bone sarcoma survivors. Use of health services, health and marital status, alcohol and smoking habits, and educational qualifications were investigated for survivors who completed a questionnaire.

Results: Survivors were seven times more likely to experience all-cause mortality than expected, and there were substantial differences in risk depending on tumour type. Beyond 25 years follow-up the risk of dying from all-causes was comparable to the general population. This is in contrast to dying before 25 years where the risk was 12.7-fold that expected. Survivors were also four times more likely to develop a SPN than expected, where the excess was restricted to 5–24 years post diagnosis. Increased health-care usage and poor health status were also found. Nonetheless, for some psychosocial outcomes survivors were better off than expected.

Conclusions: Up to 25 years after 5-year survival, bone sarcoma survivors are at substantial risk of death and SPNs, but this is greatly reduced thereafter. As 95% of all excess deaths before 25 years follow-up were due to recurrences and SPNs, increased monitoring of survivors could prevent mortality. Furthermore, bone and breast SPNs should be a particular concern. Since there are variations in the magnitude of excess risk depending on the specific adverse outcome under investigation and whether the survivors were initially diagnosed with osteosarcoma or Ewing sarcoma, risks need to be assessed in relation to these factors. These findings should provide useful evidence for risk stratification and updating clinical follow-up guidelines.

Primary malignant bone sarcomas account for 4.8% of all childhood cancers in the United Kingdom (Stiller, 2007). Approximately 65 cases occur each year, of which the principal tumour types are osteosarcoma (53%) and Ewing sarcoma (39%) (Stiller, 2007). Although the incidence is low, survival after bone sarcoma has increased substantially. Since the 1970s 5-year survival

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has risen from 23 to 64% mainly due to the introduction of modern chemotherapy (Stiller, 2007). Consequently, as the number of individuals treated for childhood bone sarcomas increases, it becomes even more important to investigate the risk of the long-term effects of this childhood cancer and its treatment.

This study assessed adverse outcomes among bone sarcoma survivors diagnosed between the ages of 0 and 14 years within the British Childhood Cancer Survivor Study (BCCSS). Key advantages of the BCCSS compared with other studies are that it is a large, population-based cohort with 30.4% of individuals diagnosed with bone sarcoma surviving to age 45 years at least. Therefore, adverse health and social outcomes beyond 35 years post diagnosis in these childhood cancer survivors can be examined much more satisfactorily than has been possible in previous smaller or non-population-based studies with limited follow-up (Gianinazzi *et al*, 2013; Jazbec *et al*, 2004; Cardous-Ubbink *et al*, 2007; Armstrong *et al*, 2009; Casagranda *et al*, 2013). In this study, we investigated the long-term risk of premature mortality, developing a subsequent primary neoplasm, health-care usage, health and marital status, alcohol and smoking habits, and educational attainment among 5-year childhood bone sarcoma survivors.

MATERIALS AND METHODS

British Childhood Cancer Survivor Study. The BCCSS, which has been described previously in detail (Hawkins *et al*, 2008), is a population-based cohort comprised of 17 980 individuals; it includes 664 bone sarcoma survivors diagnosed with cancer before the age of 15, between 1940 and 1991 in Great Britain, and who have survived at least 5 years. The cohort was ascertained through the National Registry of Childhood Tumours, which has a high estimated level of completeness (~99%) (Kroll *et al*, 2011). Ethical approval for the study was obtained from a Multi-Centre Research Ethics Committee and every Local Research Ethics Committee in Britain.

When treatment exposures within this cohort were investigated across 5-year calendar year bands, we found that before 1976, where our radiotherapy and chemotherapy treatment completeness was 98.4% and 88.4%, respectively, the majority of bone sarcoma survivors received radiotherapy (76.3%), with only a small proportion receiving chemotherapy. A distinct change in treatment practice was then observed from 1976 onwards where broadly all survivors received chemotherapy and Ewing sarcoma survivors additionally received radiotherapy. Thus, in order to address the incompleteness of treatment information in more recent diagnosis years, which was due to decreasing availability of recorded radiotherapy and chemotherapy details at the National Registry of Childhood Tumours during this period, our analyses were undertaken for bone sarcoma survivors overall and separately for osteosarcoma and Ewing sarcoma, which serve as proxies for treatment exposures. Therefore, osteosarcoma survivors were likely to have received radiotherapy if diagnosed before 1976 and only chemotherapy if diagnosed from 1976 onwards, whereas all Ewing sarcoma survivors were likely to have received radiotherapy, with only those diagnosed after 1976 additionally receiving chemotherapy. Consequently, those surviving beyond 25 years from 5-year survival were likely to have only received radiotherapy, whilst those with <25 years follow-up were likely to have received only chemotherapy or chemotherapy and radiotherapy depending on tumour type.

Record linkage ascertained outcomes. Deaths and subsequent primary neoplasms (SPNs) were ascertained for the entire BCCSS cohort through record linkage with the National Health Service Information Centre, which includes the population-based national death and cancer registries. This linkage ensures that the BCCSS is notified whenever a survivor has died or developed a SPN. To determine the expected number of deaths or incident cancers, person-years for each sex-specific, age-specific (5-year bands), and calendar year-specific (1-year bands) stratum were multiplied by the corresponding general population rates for specific cause(s) of death and incident cancers occurring throughout England and Wales.

Cause-specific mortality. For our mortality analysis, the death certificate and underlying cause of death, as coded by the Office for National Statistics using the relevant *International Classification of Disease,* were obtained. The underlying cause of death was then confirmed by a clinician using available medical records. Time at risk started at 5-year survival and continued until individuals exited from risk at the first occurrence of emigration, death, or 31 December 2010 which was the date of the most recent vital status update on the entire cohort from the National Health Service Information Centre. The standardised mortality ratio (SMR) was defined as the ratio of observed to expected number of deaths. The absolute excess risk (AER) was defined as the observed minus the expected number of deaths divided by person-years at risk multiplied by 10 000. Cumulative mortality for a specific cause of death was calculated by treating other causes of death as competing risks.

Subsequent primary neoplasms. Confirmation of all SPNs was undertaken by writing to the relevant clinician(s) to obtain diagnostic reports to confirm site, type and date of diagnosis. Time at risk for a SPN began at 5-year survival and individuals exited from risk at the first occurrence of an SPN, emigration, death, or 31 December 2006 which was the most recent date up to which all potential SPNs had been ascertained and validated. Standardised incidence ratios (SIRs) were calculated as the ratio of observed to expected number of neoplasms. The AERs were calculated as described previously for the mortality analyses. Cumulative incidence for the first occurrence of a SPN was computed treating death as a competing risk.

Questionnaire ascertained outcomes. Health-care usage, health and marital status, alcohol and smoking habits, and educational attainment were obtained via the BCCSS questionnaire. To be eligible to receive the BCCSS questionnaire survivors in the cohort had to be alive and aged at least 16 years at questionnaire send-out (median year 2002). Of the 664 bone sarcoma survivors, 506 survivors met this eligibility criteria and were contacted; amongst survivors who were ineligible, the majority had died before the questionnaire send-out ($n=106$). Ultimately, 411 (81.2%) returned a completed questionnaire. All comparisons with the general population were adjusted for age and sex. Some outcomes were adjusted further—see tables for details.

Health-care usage. Four types of health-care usage were assessed: talking to a doctor, attending the hospital outpatient department, being hospitalised as a day patient, and being hospitalised as an inpatient. In order to compare health-care use with the general population, the 2002 General Household Survey (GHS) served as the general population sample (Richards *et al*, 2004). Multivariable generalised estimating equation (GEE) logistic regression modelling was used to calculate odds ratios (ORs) for health-care usage among bone sarcoma survivors compared to that expected from the general population sample (Rebholz *et al*, 2011).

Psychosocial outcomes. The survivors' education level, smoking history, and alcohol consumption were compared with the general population using the 2002 GHS (Richards *et al*, 2004) as the reference sample, whereas marital status was compared with the National Marriage Registry (Office for National Statistics, 2002). Multivariable GEE logistic regression was used to compare educational attainment, smoking status, and alcohol use between survivors and the general population sample (Frobisher *et al*, 2007;

Frobisher *et al*, 2008; Frobisher *et al*, 2010; Lancashire *et al*, 2010). ORs were calculated using pooled Mantel–Haenszel tests to compare marital status between survivors and the general population sample.

Health status. Version one of the Short Form 36 (SF-36) Health Survey was used to measure self-reported health status by the following eight scales: physical function, role-physical, role-emotional, social functioning, mental health, vitality, pain, and general health perception. External comparisons were conducted using the Oxford Healthy Life Survey (OHLS) as the general population sample. Multivariable linear regression and direct standardisation were used to compare bone sarcoma survivors and the OHLS population.

All analyses were undertaken using Stata 12.1 (StataCorp, College Station, TX, USA). Statistical significance was defined as a two-sided P-value < 0.05.

RESULTS

Cohort characteristics. Of the 664 bone sarcoma survivors, 309 (46.5%) were diagnosed with osteosarcoma, 260 (39.2%) were diagnosed with Ewing sarcoma, 26 (3.9%) were diagnosed with chondrosarcoma, 48 (7.2%) were diagnosed with other specified bone sarcomas (e.g., fibromatous neoplasms, giant cell tumours, chordomas, and miscellaneous bone tumours), and 21 (3.2%) were diagnosed with an unspecified bone sarcoma. The mean age at diagnosis was 10.8 and the average attained age was 39.4 years (Table 1). Osteosarcoma survivors were older at diagnosis and had a higher attained age compared with Ewing sarcoma survivors. Excluding missing information, 60.2% and 60.0% of survivors received radiotherapy and chemotherapy, respectively. In general, characteristics of the 411 survivors who returned a questionnaire were similar both overall and by tumour type to the entire BCCSS bone sarcoma cohort, except that only 3.7% had died by 31 December 2010 subsequent to completing a questionnaire.

Record linkage ascertained data

Cause-specific mortality. Overall, bone sarcoma survivors experienced seven times (SMR: 7.0, 95% confidence interval (CI): 5.9–8.3) the number of deaths expected from the general population with 72 (95% CI: 57.2–85.8) excess deaths per 10 000 person-years (Table 2). The largest excess was for neoplastic-related causes in

Table 1. Characteristics of bone sarcoma study population overall and by tumour type

	Available survivors for data linkage ($N = 664$)			Available questionnaire completed survivors ($N = 411$)		
Characteristic	All *N* (%)	Osteosarcoma *n* (%)	Ewing sarcoma *n* (%)	All *N* (%)	Osteosarcoma *n* (%)	Ewing sarcoma *n* (%)
Sex						
Male	345 (52.0)	150 (48.5)	138 (53.1)	200 (48.7)	96 (47.8)	74 (48.1)
Female	319 (48.0)	159 (51.5)	122 (46.9)	211 (51.3)	105 (52.2)	80 (52.0)
Cancer site						
Upper limbs	92 (13.9)	34 (11.0)	48 (18.5)	56 (13.7)	21 (10.5)	32 (20.8)
Lower limbs	436 (65.7)	262 (84.8)	132 (50.8)	273 (66.5)	170 (84.6)	75 (48.7)
Bones of skull and face	42 (6.4)	5 (1.6)	10 (3.9)	26 (6.3)	4 (2.0)	6 (3.9)
Vertebral column	24 (3.6)	3 (1.0)	15 (5.8)	13 (3.2)	3 (1.5)	7 (4.6)
Rib, sternum, clavicle	28 (4.2)	1 (0.3)	25 (9.6)	20 (4.9)	1 (0.5)	17 (11.0)
Pelvic, sacrum, coccyx	33 (5.0)	2 (0.7)	27 (10.4)	19 (4.6)	2 (1.0)	15 (9.7)
Other	9 (1.4)	2 (0.7)	3 (1.2)	4 (1.0)	0 (0)	2 (1.3)
Age at diagnosis						
Mean (range)	10.8 (0.1–15.0)	11.5 (2.3–15.0)	10.2 (1.5–15.0)	10.8 (1.3–15.0)	11.6 (3.2–15.0)	10.0 (2.0–15.0)
0–4 years	40 (6.0)	8 (2.6)	22 (8.5)	22 (5.4)	4 (2.0)	13 (8.4)
5–9 years	185 (27.9)	74 (24.0)	84 (32.3)	122 (29.7)	46 (22.9)	58 (37.7)
10–14 years	439 (66.1)	227 (73.5)	154 (59.2)	267 (65.0)	151 (75.1)	83 (53.9)
Attained age at exit						
Mean (range)	39.4 (7.5–76.8)[a]	40.9 (10.0–71.9)[a]	35.7 (7.5–65.2)[a]	43.3 (22.4–76.8)[b]	44.6 (22.9–71.9)[b]	39.4 (22.4–65.2)[b]
16–24 years	89 (13.4)	31 (10.0)	47 (18.1)	71 (17.3)	23 (11.4)	43 (27.9)
25–34 years	155 (23.3)	62 (20.1)	78 (30.0)	169 (41.1)	83 (41.3)	72 (46.8)
35–44 years	218 (32.8)	108 (35.0)	90 (34.6)	92 (22.4)	53 (26.4)	25 (16.2)
45+ years	202 (30.4)	108 (35.0)	45 (17.3)	79 (19.2)	42 (20.9)	14 (9.1)
Radiotherapy[c]						
No	201 (39.8)	150 (59.3)	17 (9.9)	125 (40.3)	98 (58.3)	10 (10.5)
Yes	304 (60.2)	103 (40.7)	154 (90.1)	185 (59.7)	70 (41.7)	85 (89.5)
Chemotherapy[c]						
No	195 (40.0)	93 (37.5)	40 (23.8)	109 (36.7)	58 (35.6)	16 (17.2)
Yes	292 (60.0)	155 (62.5)	128 (76.2)	188 (63.3)	105 (64.4)	77 (82.8)
Surgery[c]						
No	160 (31.3)	34 (13.2)	109 (63.4)	93 (29.4)	19 (11.1)	62 (64.6)
Yes	352 (68.8)	223 (86.8)	63 (36.6)	223 (70.6)	152 (88.9)	34 (35.4)
Vital status[a]						
Alive	533 (80.3)	256 (82.9)	203 (78.1)	396 (96.4)	193 (96.0)	150 (97.4)
Dead	131 (19.7)	53 (17.2)	57 (21.9)	15 (3.7)	8 (4.0)	4 (2.6)

[a]Age at 31 December 2010 or death/embarkation (if before 31 December 2010)—relevant to the mortality analyses.
[b]Age at questionnaire completion—relevant to outcomes measured by the questionnaire.
[c]Missing data: radiotherapy (all data linkage) = 139, radiotherapy (all questionnaire) = 101; chemotherapy (all data linkage) = 157, chemotherapy (all questionnaire) = 114; surgery (all data linkage) = 152, Surgery (all questionnaire) = 95.

Table 2. All-cause and cause-specific[a] standardised mortality ratios and absolute excess risk for bone sarcoma survivors within the British Childhood Cancer Survivor Study (BCCSS) overall and by tumour type

Underlying cause of death	All bone sarcoma survivors									Osteosarcoma survivors					Ewing sarcoma survivors				
	Overall				<25 Years follow-up[b]			⩾25 Years follow-up[b]		Overall					Overall				
	Person-years	O/E	SMR (95% CI)	AER (95% CI)[c]	O/E	SMR (95% CI)	AER (95% CI)[c]	O/E	SMR (95% CI)	AER (95% CI)[c]	Person-years	O/E	SMR (95% CI)	AER (95% CI)[c]	Person-years	O/E	SMR (95% CI)	AER (95% CI)[c]	P-value[d]
All-causes	15 678	131/18.7	7.0 (5.9, 8.3)	71.6 (57.3, 86.0)	115/9.1	12.7 (10.5, 15.2)	82.7 (66.3, 99.1)	16/9.6	1.7 (1.0,2.7)	22.3 (−5.0,49.7)	7539	53/8.9	6.0 (4.5, 7.8)	58.5 (39.6, 77.5)	5327	57/4.6	12.3 (9.4, 16.0)	98.3 (70.6, 126.1)	<0.001
Recurrence	15 678	80/0.0	NA	51.0 (39.8, 62.2)	79/0.0	NA	61.6 (48.1,75.2)	1/0.0	NA	3.5 (−3.4, 10.3)	7539	26/0.0	NA	34.5 (21.2, 47.7)	5327	42/0.0	NA	78.8 (55.0, 102.7)	
SPN	15 678	31/5.5	5.6 (3.8, 8.0)	16.2 (9.3, 23.2)	24/1.7	14.4 (9.2, 21.5)	17.4 (9.9, 24.9)	7/3.9	1.8 (0.7, 3.7)	10.9 (−7.2, 29.0)	7539	18/2.7	6.7 (4.0, 10.6)	20.3 (9.3, 31.3)	5327	8/1.1	7.1 (3.1, 14.1)	12.9 (2.5, 23.3)	0.772
Circulatory	15 678	8/3.6	2.3 (1.0, 4.4)	2.8 (−0.7, 6.4)	3/1.0	3.0 (0.6, 8.7)	1.6 (−1.1, 4.2)	5/2.5	2.0 (0.6, 4.6)	8.6 (−6.7, 23.9)	7539	3/1.7	1.8 (0.4, 5.3)	1.8 (−2.7, 6.3)	5327	2/0.7	3.0 (0.4, 11.0)	2.5 (−2.7, 7.7)	0.598
External	15 678	5/4.7	1.1 (0.3, 2.5)	0.2 (−2.6, 3.0)	5/3.9	1.3 (0.4, 3.0)	0.8 (−2.6, 4.3)	0/–	NP	NP	7539	3/2.2	1.4 (0.3, 4.0)	1.0 (−3.5, 5.5)	5327	1/1.6	0.6 (0.0, 3.6)	−1.0 (−4.7, 2.6)	0.535

Abbreviations: AER = absolute excess risk; CI = confidence intervals; E = expected number; NA = not applicable; NP = not possible to reliably calculate due to very small expected number; O = observed number; SMR = standardised mortality ratios.
[a]Results are only reported for underlying causes of deaths with at least five observed events overall. Other causes of death were: four genitourinary, one digestive, one infection, and one unknown.
[b]From five-year survival.
[c]Per 10 000 person-years.
[d]Comparing SMRs for osteosarcoma and Ewing sarcoma survivors.
SMRs and AERs where there are <5 observed events should be interpreted with caution.

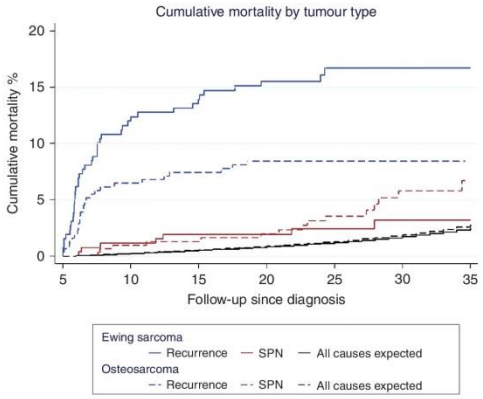

Figure 1. Cumulative mortality of recurrence and second primary neoplasms among childhood bone sarcoma survivors within the British Childhood Cancer Survivor Study (BCCSS) by tumour type.

both relative and absolute terms; recurrences and SPNs accounted for 71.2% and 22.6% of all excess deaths, respectively. When the SMR was assessed by follow-up, a striking difference was observed; the overall SMR was 12.7-times (95% CI: 10.5–15.2) that expected during 0–24 years follow-up and only 1.7-times (95% CI:1.0–2.7) that expected beyond 25 years. Notably, there was an 8-fold decrease in SMRs from 0–24 years to beyond 25 years follow-up for SPN-related deaths. Compared with the general population, the SMR for all-causes was significantly higher ($P<0.001$) for Ewing sarcoma survivors, who had approximately double the SMR and AER of osteosarcoma survivors. Although recurrence and SPN-related deaths accounted for ~93% of all excess deaths in both tumour types, there was heterogeneity in the proportion of recurrence and SPN excess deaths; recurrences accounted for 59.0% and 80.2% of excess deaths in osteosarcoma and Ewing sarcoma survivors, respectively, whilst the corresponding excess SPN deaths were 34.7% and 13.1%.

There was a steep increase in mortality during the initial 5 years following 5-year survival where the cumulative mortality reached 10.4% (95% CI: 8.3–13.0) (Supplementary Figure 1). Subsequently, there was a more gradual incline to 20.6% (95% CI: 17.3–24.3) at 35 years post diagnosis. When stratified by tumour type (Figure 1) a significant difference ($P=0.004$) in cumulative mortality was observed for recurrences, where Ewing sarcoma survivors had nearly double the cumulative mortality at 35 years post diagnosis (osteosarcoma: 8.5% *vs* Ewing sarcoma: 16.7%). Conversely, the cumulative mortality due to SPNs was twice as high for osteosarcoma compared with Ewing sarcoma survivors at the same point (osteosarcoma: 6.7% *vs* Ewing sarcoma: 3.2%).

Subsequent primary neoplasms. Bone sarcoma survivors were 4.4-times (95% CI: 3.3–5.8) more likely to experience a SPN than expected and had 29.3 (95% CI: 18.7–39.9) excess SPNs per 10 000 person-years (Table 3). By SPN cancer type, survivors overall and by tumour type were at a considerably higher risk of developing a subsequent bone neoplasm and to a lesser extent a breast neoplasm. Specifically overall, survivors were 136.3- (95% CI: 79.2–234.8) and 4.5-times (95% CI: 2.6–8.0) more at risk than the general population for bone and breast cancers, respectively. When the SIRs were assessed by follow-up, a 8.4-fold (95% CI: 6.1–11.2) increased risk was observed during 0–24 years, where the SIR for subsequent breast and bone cancer were 10.8 (95% CI: 5.2–19.9) and 154.3 (95% CI: 82.2–263.8), respectively. Beyond 25 years of

Table 3. Overall and site-specific[a] standardised incidence ratios and absolute excess risks of second primary neoplasms for bone sarcoma survivors within the British Childhood Cancer Survivor Study (BCCSS)

	All bone sarcoma survivors															
	Overall			<25 Years follow-up[b]			⩾25 Years follow-up[b]			Osteosarcoma survivors			Ewing sarcoma survivors			
SPN	O/E	SIR (95% CI)	AER (95% CI)[c]	O/E	SIR (95% CI)	AER (95% CI)[c]	O/E	SIR (95% CI)	AER (95% CI)[c]	O/E	SIR (95% CI)	AER (95% CI)[c]	O/E	SIR (95% CI)	AER (95% CI)[c]	*P*-value[d]
Any cancer site	49/11.2	4.4 (3.3, 5.8)	29.3 (18.7, 39.9)	44/5.3	8.4 (6.1, 11.2)	34.7 (23.1, 46.3)	5/5.9	0.8 (0.3, 2.0)	−5.1 (−30.2, 20.0)	23/6.0	3.9 (2.6, 5.8)	26.1 (11.7, 40.5)	19/2.8	6.7 (5.3, 10.6)	35.7 (16.9, 54.6)	0.070
Breast	12/2.6	4.5 (2.6, 8.0)	7.2 (2.0, 12.5)	10/0.9	10.8 (5.2, 19.9)	8.1 (2.6, 13.7)	2/1.7	1.2 (0.1, 4.2)	1.6 (−14.2, 17.5)	6/1.5	4.0 (1.8, 8.8)	6.9 (−0.5, 14.2)	5/0.6	7.8 (3.2, 18.6)	9.6 (−0.1, 19.3)	0.236
Bone	13/0.1	136.3 (79.2, 234.8)	10.0 (4.5, 15.5)	13/0.1	154.3 (82.2, 263.8)	11.6 (5.2, 17.9)	0/–	NP	NP	3/0.05	65.4 (21.1, 202.7)	4.5 (−0.7, 9.7)	8/0.04	223.0 (111.5, 445.9)	17.6 (5.4, 29.8)	0.057

Abbreviations: AER = absolute excess risk; CI = confidence intervals; *E* = expected number; NA = not applicable; NP = not possible to reliably calculate due to very small expected number; O = observed number; SIR = standardised incidence ratios; SMR = standardised mortality ratios.

[a]Results are only reported for site-specific SPNs with at least five observed events overall. Other SPNs were: four genitourinary, four bladder, three digestive, three connective and soft tissue, three malignant neoplasms with unspecified sites, two gliomas, two Hodgkin lymphoma, two NHL, two leukemia, one respiratory, one eye, one thyroid.

[b]From five-year survival.

[c]AER is shown per 10 000 person-years.

[d]Comparing SIRs for osteosarcoma and Ewing sarcoma survivors.

SIRs and AERs where there are <5 observed events should be interpreted with caution.

follow-up, the SIR for any SPN was not significantly higher in survivors than expected from the general population.

There was a continuous and steady increase in cumulative incidence for SPNs over follow-up, ultimately reaching 8.3% (95% CI: 5.9–11.2) at 30 years post diagnosis (Supplementary Figure 2). When stratified by tumour type, the cumulative incidence curves were nearly identical to each other and to bone sarcoma survivors overall ($P > 0.05$).

Questionnaire ascertained data

Health-care usage. Compared with the general population sample, bone sarcoma survivors were almost three times (OR: 2.9, 95% CI: 2.3–3.7) more likely to have visited an outpatient hospital department in the previous three months (Table 4). Survivors were also over twice (OR: 2.4, 95% CI: 1.7–3.4) more likely to be hospitalised as an inpatient during the previous year than the general population sample. When analysed by tumour type, both osteosarcoma and Ewing sarcoma survivors had significantly higher odds of attending the hospital as an outpatient or inpatient than expected.

Psychosocial outcomes. Bone sarcoma survivors overall were comparable to the general population sample for being ever-married, a current drinker, or consuming harmful amounts of alcohol (Table 4). Survivors were, however, significantly less likely to be a current smoker (OR: 0.6, 95% CI: 0.5–0.8) and consume alcohol over recommendations (OR: 0.7, 95% CI: 0.5–0.9) than the general population sample. Compared to that expected, survivors performed well in obtaining educational qualifications and were 70% more likely to have obtained at least O-levels (OR: 1.7, 95% CI: 1.3–2.1). When analysed by tumour type, the odds for each psychosocial outcome were comparable to the overall finding.

Health status. Compared with the general population sample, bone sarcoma survivors overall were significantly more limited in all SF-36 scales with the exception of role-emotional (Figure 2). The most notable differences occurred in physical function, role-physical, and pain. For the individual components of the physical function scale (Supplementary Figure 3), 54% and 61% of survivors were limited in 'moderate activities' and 'walking more than one mile' compared with the 8% and 11% expected from the general population sample, respectively. In the role-physical scale (Supplementary Figure 4), the largest difference between the survivors and general population sample was in 'being limited in the kind of work and activities', although all component questions reported at least a 10% deficit. Finally, for the pain scale (Supplementary Figure 5), survivors reported more bodily pain (12% *vs* 5%) and more pain interference (16% *vs* 5%) during the past 4 weeks compared with the general population sample.

When stratified by tumour type, osteosarcoma survivors were assessed additionally by amputation status, where only arm or leg amputations as a form of initial treatment for the first primary tumour were included. Compared with the general population sample, osteosarcoma amputee survivors reported being the most limited in all scales relative to osteosarcoma non-amputees and Ewing sarcoma survivors, with a significantly ($P < 0.001$) higher disadvantage in physical function (Figure 2).

DISCUSSION

This is the first large-scale population-based study to provide a comprehensive description of long-term health and social outcomes among a large cohort of 5-year bone sarcoma survivors, both overall and by tumour type, beyond 35 years post diagnosis. Mortality estimates in this cohort were elevated seven times that expected and

Table 4. Percentages and odds ratios (with corresponding 95% CIs) for the likelihood of use of health services and psychosocial outcomes in bone sarcoma survivors within the British Childhood Cancer Survivor Study (BCCSS) compared with the general population of Britain

	UK norms (ref)	Bone sarcoma overall OR (95% CI)	Osteosarcoma OR (95% CI)	Ewing sarcoma OR (95% CI)
Marital Status[a]				
Males ever-married	1.0	0.7 (0.5, 1.0)	1.0 (0.6, 1.6)	0.7 (0.4, 1.3)
Females ever-married	1.0	0.8 (0.6, 1.1)	0.8 (0.5, 1.2)	0.9 (0.6, 1.4)
Education[b]				
University degree or higher	1.0	1.2 (1.0, 1.6)	1.5 (1.1, 2.1)	1.0 (0.8, 1.5)
Teaching qualification or higher	1.0	1.1 (0.9, 1.4)	1.3 (1.0, 1.7)	1.0 (0.7, 1.4)
A-levels or higher[c]	1.0	1.2 (1.0, 1.5)	1.2 (0.9, 1.6)	1.1 (0.8, 1.5)
O-levels or higher[d]	1.0	1.7 (1.3, 2.1)	1.8 (1.2, 2.6)	2.0 (1.2, 3.1)
Alcohol[e]				
Current drinker	1.0	0.8 (0.6, 1.1)	1.0 (0.6, 1.6)	0.8 (0.5, 1.3)
Consuming over recommendations	1.0	0.7 (0.5, 0.9)	0.7 (0.5, 1.1)	0.5 (0.3, 0.9)
Consuming harmful amounts	1.0	0.7 (0.4, 1.1)	0.6 (0.3, 1.4)	0.7 (0.3, 1.5)
Smoking[e]				
Current smoker	1.0	0.6 (0.5, 0.8)	0.7 (0.5, 1.0)	0.6 (0.4, 0.9)
Use of health services[f]				
Talked to a doctor[g]	1.0	1.2 (0.9, 1.6)	1.3 (0.9, 1.8)	1.2 (0.8, 1.8)
Attended as outpatient[g]	1.0	2.9 (2.3, 3.7)	2.9 (2.1, 4.0)	3.2 (2.2, 4.7)
Attended as day patient[h]	1.0	1.1 (0.7, 1.5)	1.2 (0.7, 1.9)	1.0 (0.6, 1.8)
Attended as inpatient[h]	1.0	2.4 (1.7, 3.4)	2.5 (1.6, 3.9)	2.8 (1.7, 4.7)

Abbreviations: OR = odds ratio; CI = confidence interval.
[a]From a pooled Mantel–Haenszel model controlling for attained age.
[b]From a GEE multivariable logistic regression controlling for age at questionnaire completion and sex (taking into account the GHS weighting factor).
[c]Degree received at age 16.
[d]Degree received at age 18.
[e]From a GEE multivariable logistic model adjusting for attained age (⩽69 years), sex, marital status, socioeconomic classification, educational attainment, and region (taking into account the GHS weighting factor).
[f]From a GEE multivariable logistic model adjusting for age at questionnaire completion, sex, and educational attainment.
[g]Excluding women who were pregnant at time of survey.
[h]Excluding visits for having a baby.

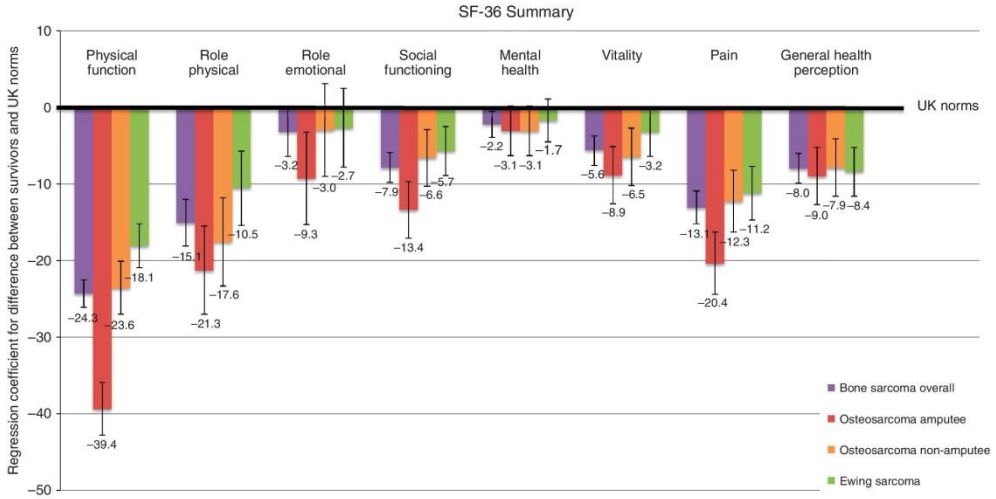

Figure 2. Sex and age adjusted regression coefficients and corresponding 95% confidence intervals for differences in SF-36 health status scales between bone sarcoma, osteosarcoma amputees, osteosarcoma non-amputees, and Ewing sarcoma survivors *vs* UK norms.

varied significantly between tumour types, which were consistent with previous findings of a large-scale US study (Armstrong *et al*, 2009). Past studies have also shown the principal cause of death was neoplastic-related (MacArthur *et al*, 2007; Ginsberg *et al*, 2010; Nagarajan *et al*, 2011). However, to our knowledge, this is the first study that has shown substantial differences when comparing excess

and cumulative mortality between tumour types; osteosarcoma survivors had double the cumulative mortality for SPNs compared with Ewing sarcoma and Ewing sarcoma survivors had double the cumulative mortality for recurrences compared with osteosarcoma at 35 years post diagnosis. The osteosarcoma survivors in this study were much more likely to have an amputation than Ewing sarcoma, which may partially explain why osteosarcoma survivors were less likely to have recurred (Grimer *et al*, 2002). Additionally, due to the extended follow-up available, this is the first study to show that beyond 25 years follow-up the risk of dying from all-causes is comparable to the general population and unlikely to exceed 2.7-fold that expected. This is in contrast to dying before 25 years of follow-up, where the risk is 12.7-fold that expected. This provides important evidence for clinicians who monitor survivors treated in similar decades to those included in the BCCSS. A possible explanation for this striking absence or low risk of excess mortality with extended follow-up may relate to our previous observation that, as the overall cohort of childhood cancer survivors ages, a large proportion of excess deaths are attributed to SPNs (Reulen *et al*, 2010), particularly breast, digestive, genitourinary, and lung carcinomas. Although carcinomas of these sites are common cancers of adulthood in the general population, in childhood cancer survivors they are principally caused by direct radiotherapy exposure (Reulen *et al*, 2011). As 80% of the bone sarcomas included here were diagnosed in the limb, there is unlikely to have been much direct exposure from radiotherapy to tissues of these sites due to the lack of proximity of the radiotherapy fields.

The overall and tumour type-specific SIRs for SPNs were consistent with previous studies (Magnani *et al*, 1996; Cardous-Ubbink *et al*, 2007; Inskip and Curtis, 2007; Friedman *et al*, 2010). Additionally, our findings are consistent with previous literature in that the most common SPN was breast cancer for osteosarcoma survivors and bone cancer for Ewing sarcoma survivors (Inskip and Curtis, 2007). Due to the extended follow-up available, this is the first study to show that the risk of developing SPNs was 9.9-fold the expected during 0–24 years follow-up and comparable to the general population beyond 25 years follow-up, where it was unlikely to exceed 2.0-fold that expected. Notably, all thirteen bone cancers occurred before 25 years follow-up, nine of which developed inside or on the edge of tissue directly irradiated to treat the original bone sarcoma and one in a survivor diagnosed with a p53 mutation. This corresponds with our previous work that found that bone cancer is the most common SPN after a first primary bone sarcoma (Reulen *et al*, 2011), which is principally attributable to exposure of the SPN site to radiation during treatment for the first cancer (Tucker *et al*, 1987; Hawkins *et al*, 1996; Schwartz *et al*, 2014). Of the two breast cancers observed subsequent to 25 years follow-up, both developed in survivors previously treated for a bone sarcoma of a lower limb with unknown p53 status.

Consistent with other studies (Eiser *et al*, 2001; Hudson *et al*, 2003; Zeltzer *et al*, 2008), we reported that survivors were severely limited in health status, in particular physical function and pain. Although previous studies have suggested that health status among amputees is generally similar to non-amputees (Eiser and Grimer, 1999; Nagarajan *et al*, 2004; Paul, 2008; Eiser, 2009; Nagarajan *et al*, 2009; Barrera *et al*, 2012), we found that osteosarcoma amputees reported the worst health status for all scales, with significantly higher limitations in physical function relative to osteosarcoma non-amputees and Ewing sarcoma (95% of which were non-amputees) survivors.

Although we report here on appreciable proportions of the bone sarcoma survivors experiencing detrimental effects to their health, many of their social outcomes were favourable. In fact, our findings suggest that survivors were more likely than expected to obtain some types of educational qualification and less likely to be a current smoker than expected from the general population.

Current guidelines and recommendations. The Bone Cancer Research Trust currently recommends yearly follow-up after 5-year survival (Newby and Unsworth, 2013a, 2013b). From the evidence presented here, 74% and 21% of all excess deaths before 25 years of follow-up were due to recurrence and SPN, respectively, and therefore monitoring of survivors for recurrences and SPNs, particularly during the period 5–10 years post diagnosis where risk of recurrence is highest, could help prevent premature mortality. Bone and breast SPNs should also be a particular concern and regular follow-up should be provided, particularly in the period 0–24 years following 5-year survival for bone SPNs. Factsheets given to childhood cancer survivors could further expand upon the risk of recurrence and SPNs and the potential for early diagnosis by detailing more precisely signs and symptoms relating to bone and breast neoplasms. Furthermore, the substantial excess risks of specific physical limitations and pain are likely to be useful for risk stratification and possible interventions that seek to reduce morbidity and the practical difficulties that survivors may face.

Limitations. Although the findings in this paper may not be generalisable for children diagnosed after 1991, the purpose of this study was to address the long-term, beyond 35 years post diagnosis, outcomes that childhood bone sarcoma survivors are currently facing. We acknowledge reassessment is necessary and recommend further analyses to be conducted on the recently extended BCCSS cohort, which includes 5-year survivors diagnosed from 1992 to 2006. Furthermore, as a large proportion of bone sarcoma diagnoses occur in individuals aged over 14 years, we recommend further analyses on adverse outcomes to be assessed using the Teenage and Young Adult Cancer Survivor Study (TYACSS), which we have established recently and includes all 5-year survivors diagnosed from age 15–39 in England and Wales between 1970 and 2006. Finally, a potential limitation of our study is the lack of detailed treatment information. Although we report a large reduction in excess mortality and SPNs beyond 25 years follow-up, those followed-up for <25 years are more likely to be treated differently due to the introduction of chemotherapy. Thus, reassessment of these more recently diagnosed individuals is essential in order to determine whether the decreases in risk reported in this study remain with newer treatment practices. Nevertheless, due to our population-based design, the evidence presented here provides a reliable and unbiased basis to update clinical follow-up guidelines in relation to bone sarcoma survivors diagnosed before age 15 and treated before 1992 in Great Britain by using cancer diagnosis as a proxy.

CONCLUSIONS

In conclusion, childhood bone sarcoma survivors diagnosed between 1940 and 1991 in this cohort are at substantial risk of death and SPNs up to 25 years after 5-year survival, but the risk is greatly reduced thereafter. Survivors additionally face difficulties in daily life due to their excess prevalence of poor physical health status. As there are variations in the degree of excess depending on the specific outcome and whether they survived osteosarcoma or Ewing sarcoma, risk needs to be assessed in a stratified way. These findings should provide useful evidence for risk stratification, updating clinical follow-up guidelines, and possible intervention studies.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DISCLAIMER

The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

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