

Cancer in Children and Young People

The Cancer in Children and Young People set of articles is separated into 12 sections, each of which can be individually downloaded. It is a 'work in progress' incorporating new information whenever time permits.

Section 9

Issues affecting the survivors of childhood cancer

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Childhood Cancer

9. Issues affecting survivors of childhood cancer after treatment

Approximately 1 in 285 children in the US will be diagnosed with cancer before the age of 20 years and approximately 1 in 530 young adults between the ages of 20 and 39 years is a childhood cancer survivor (Ward [2014](#)). Cancer mortality for both children and adolescents continues to decline, however, greater than 1900 cancer deaths among children and adolescents still occur each year in the US and many survivors experience long-term effects that limit their quality of life (Smith [2014](#)). The number of survivors of childhood cancers is expected to increase in the future consequent to the lifesaving advances in treatment introduced after 1970, especially for acute lymphoblastic leukaemia. Because this population is at increased risk for illness-related morbidity and mortality, appreciating the number of survivors who were treated as children is important both to determining the national cancer burden and planning for the future health care needs of these individuals (Mariotto [2009](#)). Casillas ([2015](#)) concluded that while the incidence of late effects increases over time for survivors, the likelihood of receiving survivor-focused care decreases for vulnerable populations. There were differences in survival rates depending on factors such as living in remote areas and disadvantaged areas of Australia especially for children with leukaemia (Youlden [2011](#)).

The impact of childhood cancer goes beyond incidence and treatment factors. De Blank ([2015](#)) suggests using the years of potential life lost (YPLL) and years of life lived with disease (YLLD) in children and adolescents who died of cancer to estimate the impact of childhood cancer. The histology with the highest mean YLLD per death in children and adolescents who died of cancer was primitive neuroectodermal tumour (4.6 years lived). CNS tumours are the most common solid malignancy in individuals less than 20 years old and have the highest YPLL cost of all cancers.

Five year survival rates among childhood cancer have risen to 80%. Relapses are rare after five years of remission. Long term follow-up should also detect treatment related late adverse effects. Repeated cardiac evaluations are necessary, due to cumulative dose dependent cardiotoxicity of anthracycline. Endocrinological disorders and problems of fertility are mainly related to radiotherapy or high dose chemotherapy. Bone mineral density can be altered. Cognitive function, academic level and social outcome of irradiated patients and patients treated for cerebral tumours should be closely assessed and helped (Kahalley [2016](#)). Second neoplasms related to previous treatments may occur. One of the major on-going treatment objectives is to preserve the quality of life of cured patients, and to improve their information in the framework of a shared-care model involving the general practitioner, the adult medicine specialists and the oncologic paediatric centre (Plantaz [2014](#)).

The number of people in the UK alive after diagnosis of or treatment for cancer has risen by 500,000 in the past five years, to reach 2.5 million, the charity Macmillan Cancer Support has said (Hawkes [2015](#)). Though providing encouraging evidence of a better prognosis for people with cancer, this growing group of survivors poses problems for the NHS, the charity said.

Around a quarter of people treated for cancer face poor health or disability after treatment. Of the 2.5 million people living with cancer, 1.6 million were given their diagnosis more than five years ago, and 5 year survival is generally counted as a cure.

Skinner & Oeffinger ([2013](#)) recommend long-term follow-up of childhood cancer survivors in view of their high frequency of chronic medical problems, many of which may be serious, disabling or life-threatening. 56% of childhood cancer survivors experienced at least one late effect. Symptoms included impaired visual acuity (45%), dizziness (36%), allergies (34%), and mental retardation, cataract, suspected infertility, delayed puberty, growth hormone deficiency,

weight gain and Cushingoid features (after corticosteroid treatment, (Aljebab [2016](#)) and other audiovisual, urinary, endocrine (Ramanauskiene 2014, Leroy [2015](#)), infertility, cardiovascular, respiratory, gastrointestinal, spinal, extremity and neuromuscular problems (Ozono [2014](#)).

Printz ([2013](#)) reported the study by Hudson that 98% of 1,713 childhood cancer survivors as adults had at least 1 chronic health condition. Among the undetected health issues diagnosed were new cancers, heart and lung abnormalities, and memory and other neurocognitive problems. Approximately 80% of study participants had a life-threatening, serious or debilitating chronic condition. Participants included survivors of leukaemia and lymphoma, as well as tumours of the brain, bone and other organs. Approximately half of the survivors were diagnosed with cancer more than 25 years ago.

There were more than 11 million survivors of paediatric cancers living in the US alone in 2011 (Winick [2011](#)). We do not have the figures for the UK. Many family's lives are totally disrupted by the emotional, time and energy consequences and stress of coping with the treatment itself, the physical and emotional needs of the patient and those of everyone else concerned. There are also significant physical, emotional, neurological, educational and societal costs of survival. In Europe, up to 30% of survivors of childhood cancer have severe long-term effects of their treatment (Vassal [2014](#)).

Common challenges across the survivors included physical appearance, fertility, late effects, social relationships, and changing priorities (D'Agostino & Edelstein [2013](#)). Childhood cancer survivors struggled with identity formation, social isolation, and health care transitions. Concerns specific to survivors diagnosed as young adults (YAs) included financial independence and protecting parents. Childhood brain tumour survivors struggled with cognitive deficits (sometimes caused by cerebral microbleeds Roddy [2016](#)), limited career options, and poor social skills (Schulte & Barrera 2010, Emond [2016](#)), whereas brain tumour survivors diagnosed as YAs emphasized cognitive decline, loss of autonomy, and living with an incurable disease. Resource needs including peer support, age-specific information, and having health care providers proactively raise salient issues.

For these reasons, as well as to prevent the suffering that goes with the diagnosis of any form of cancer, it is important that the factors involved in the causation of childhood cancer become better known and prevented wherever possible. Many forms of childhood cancer can be treated effectively, some with a very high percentage chance of a 'cure' at least for several years. The longer-term consequences of surviving childhood cancer are, however, not always well known, and recommended risk-based care is not always available (Nathan [2008](#)). Kopp ([2012](#)) says that more than 60% of survivors of childhood and adolescent cancer will have at least 1 long-term side effect from treatment.

In many cases of recovery following treatment for childhood cancer, it is beneficial for parents or caregivers, to be aware of monitoring specific health and educational challenges that may arise as a result of the treatment. This will enable them better to deal with the relevant authorities. These are covered in Section 10, Parent needs.

Han ([2013](#)) suggests that younger age at diagnosis, older age at initial visit, a diagnosis of a brain tumour or lymphoma, and use of radiotherapy were significant risk factors for late effects.

Möller ([2001](#)) found that long-term survivors of childhood cancer had an increased mortality rate, mainly dying from primary cancers. The authors suggested that modern treatments have reduced late cancer mortality without increasing the rate of therapy-related deaths. However, an extended follow-up of 20,483 5-year survivors of paediatric and adolescent cancer over 4 decades indicated that excess mortality persisted long after diagnosis. At 20 years of follow-up (25 years after first cancer diagnosis), the death rate due to a subsequent malignancy exceeded that due to all other

causes (Mertens [2008](#)). Reulen ([2010](#)) also found that among a cohort of British survivors of childhood cancer, excess mortality from second primary cancers and circulatory diseases continued to occur beyond 25 years from diagnosis.

Survivors of childhood cancer have a high rate of illness owing to chronic health conditions, according to a study of 10,397 survivors where 62.3% had at least one chronic condition and 27.5% had a severe or life-threatening condition (Oeffinger [2006](#)).

Yi ([2014](#)) reports that over 73% of Korean cancer survivors reported at least one health problem. Growth issues ranked as the most frequently reported; followed by chronic fatigue, vision, learning/memory issues and weak bones. Those with learning/memory and chronic fatigue issues reported both lower physical and mental functioning. 40% of childhood cancer survivors reported chronic fatigue (Zeller [2014](#)), and these reported a significantly higher frequency of symptoms typical of chronic fatigue syndrome and symptoms of autonomic dysfunction, than those not reporting fatigue to be an issue.

In a tertiary cancer centre in South India (Rajendranath [2014](#)), the late effect of childhood cancer were impaired fertility (24.5%), impaired growth pattern (4.5%), endocrine dysfunction (4.5%), second malignancy (1.2%). 3 of 20 patients assessed had severe neurocognitive impairment. A high QoL was reported by 60% and 'average' QoL by 38%.

Funding for resource-intense programmes, transitioning care to adult clinical services (Granek [2012](#)), volume of sub-specialty referral and participation in research are common challenges (Kenney [2011](#)).

Garwicz ([2012](#)) concludes that improvement of definite survival demands not only reducing early but also late and very late mortality. These are very good reasons for preventing the cancer in the first place. There are many sociodemographic factors that determine the take-up of follow-up care. These include type of cancer; relapse; number of treatment modalities; distance from treatment centre; non-White race; public insurance (Barakat [2011](#)).

Some treatments, such as hematopoietic cell transplantation (HCT), seem to lead to more health complications later on, with unrelated donor HCT recipients being at highest risk. HCT survivors were more likely than sibling controls to have severe/life-threatening and two or more chronic health conditions, as well as functional impairment and activity limitation (Armenian [2011](#)). CNS irradiation to temporal regions were associated with a higher risk for memory impairment, and more social and general health problems, whereas exposure to frontal regions was associated with general health problems and physical performance limitations (Armstrong [2010](#)).

A study by Lorenzi ([2011](#)) found that survivors of childhood cancer, especially leukaemia, CNS tumours, bone & soft tissue sarcomas and kidney cancer, were at increased risk of many types of illnesses requiring hospitalisation, approximately 41% as against 17% of the general population. Survivor hospitalisation rates were found to be 1.6 times the US average, both male and female, especially in the 45-54 year age group (Kurt [2011](#)). Hospital emergency departments (ED) are integral to the care provided to children with cancer. 39.3% of frequent utilisers had acute lymphoblastic leukaemia (ALL) and 16.0% had central nervous system (CNS) tumours. Frequent utilisation was associated with age 1-4 years, less than 1 year, 5-9 years (in order of frequency of visits) and Hispanic ethnicity compared to white, non-Hispanics, and urban residence. Few children with cancer received no medication, laboratory, or imaging during their ED visit (Mueller [2016](#)).

There were 26,770 emergency department (ED) hospital visits by 17,943 children with cancer at 39 children's hospitals in the US during 2011-2013. Fifty-six percent of ED visits resulted in

admission. ED visits reasons including neutropenia (OR = 43.4), blood stream infection (OR = 3.3), pancytopenia (OR = 28.8), dehydration (OR = 2.3), or pneumonia (OR = 3.8) (Mueller [2015](#)).

According to Winick ([2011](#)), the group most severely impacted by their cancer and their therapies are the survivors of CNS tumours.

Low-grade glioma survivors suffer many adverse effects, including blindness, hearing loss, obesity/overweight, hyperinsulism, growth hormone deficiency, thyroid hormone deficiency, adrenocorticotrophic hormone (ACTH) deficiency and teratoid/rhabdoid tumours (Bozzai [2017](#)). Armstrong ([2011](#)) found that among 5-year survivors assessed for intellectual function, 34% had an IQ below average, associated with younger age at diagnosis, epilepsy and shunt placement.

The late effects of therapy for childhood leukaemia (Fulbright [2011](#), Bardi [2011](#), Robison [2011](#)) and CNS tumours (Brinkman [2016](#), Ehrstedt [2016](#)) include secondary malignancy, cardiotoxicity, obesity, endocrine abnormalities, reproductive changes, neurocognitive deficits and psychosocial effects. Kanda ([2015](#)) reported that ALL treatment may result in extreme spindles in the brain, which can have serious physical and mental after effects. Survivors exposed to cranial radiotherapy (CRT) are at particularly high risk for long-term morbidity, such as endocrine insufficiencies, metabolic complications, and cardiovascular morbidity (Follin & Erfurth [2016](#)).

Parents who self-reported long-term uncertainty about their child's illness were more likely to report child psychosocial difficulties (Williams [2013](#)). Parents and siblings have their own issues to cope with and overall quality of life for all concerned can be seriously impaired. Young people perceive their parents as reacting differently to cancer versus non-cancer distress, which is in turn predictive of their perceptions of growth. Findings suggest that parental support and reassurance/distraction are possible mechanisms facilitating resilience and growth in children with cancer (Howard Sharp [2016](#)).

Disease mortality from cardiovascular and respiratory illnesses was much higher than would be expected, with differences between subgroups (Prasad [2012](#)).

Survivors want to be more informed, especially on possible late effects. Those with higher information needs report higher psychological distress and lower Quality of Life (Gianinazzi [2014](#)). Raz ([2016](#)) found a difference between children diagnosed up to 12 years of age and those diagnosed during adolescence in the effect information about cancer had on their quality of life. (Participants were divided into two groups according to their age at diagnosis: from birth to 12 years old and from age 12-18). In the group diagnosed at a younger age, those who had received "good information" were found to have better quality of life, lower mental pain, and higher mental pain tolerance than did those in the same group (diagnosed at a younger age) who received "not good information." By contrast, in the group diagnosed during adolescence, those who had received "not good information" scored higher on these measures than did their counterparts who had received "good information."

Assendelft & van Boven ([2013](#)) report the need for a larger role of primary care in the guidance given to patients regarding risks & lifestyle post-treatment. Many childhood cancer survivors do not discuss their cancer history with their current primary care provider and most have no survivor care plan (Kirchhoff [2014](#)). Most general practitioners are unaware of surveillance guidelines and prefer to follow patients in collaboration with a cancer centre. In one case, cited by Suh ([2014](#)), of a young adult survivor of Hodgkin lymphoma, 90.6% practitioner respondents did not appropriately recommend yearly breast cancer surveillance, 85.1% did not appropriately recommended cardiac surveillance, and 23.6% did not appropriately recommend yearly thyroid surveillance.

Accelerated Aging

According to Edelstein ([2011](#)), adult survivors exhibit signs of early ageing regardless of how young they were at diagnosis. Females diagnosed with cancer at age 21 or younger, have rates of frailty similar to rates in older adults. Frailty among childhood cancer survivors increases risk for chronic disease and mortality. The prevalence of frailty among young adult survivors is similar to that among adults 65 years old and older, suggesting accelerated aging (Ness [2013](#)).

Cancer recurrence

Improvements in treatment over the past five decades have resulted in a cohort of more than 30,000 long-term survivors of childhood cancer in the UK with more added annually (Sugden [2014](#)).

Interruptions or discontinuations of the therapy due to drug-related toxicities, which can be life threatening, may result in an increased risk of relapse (Smid [2016](#)).

As the population of cancer survivors has increased and continues to age, the occurrence of second cancers has risen dramatically—from 9% of all cancer diagnoses in 1975-1979 to 19% in 2005-2009. A genome-wide association study of survivors of Hodgkin lymphoma who received radiotherapy identified a locus on chromosome 6q21 as being associated with second cancer risk, demonstrating that recent advances in genomics are likely to prove invaluable for elucidating the contribution of genetic susceptibility to second cancer aetiology (Morton [2014](#)).

The duration and intensity of maintenance chemotherapy may influence the risk of subsequent cancers (Schmiegelow [2011](#)). The risk of therapy-related myeloid neoplasms is below 2% for most series of treatments. This is important for younger cancer patients and during the first 5 years after the primary malignancies (Leone [2011](#)).

Multiple subsequent neoplasms are common among ageing survivors of childhood cancer (Bowers [2013](#)). Children not exposed to radiotherapy in treatment who develop subsequent neoplasms may well reveal more clues about genetic susceptibility (Armstrong [2011](#)). Shorter constitutional telomere (telomeres protect the end of chromosomes from deterioration) length has been associated with increased cancer incidence and may contribute to the likelihood of secondary cancers (Gramatges [2014](#)).

Wang ([2016](#)) suggested the necessity of a careful follow up of patients treated for ALL for the potential occurrence of central nervous system second neoplasms, especially when the patients have previously undergone cranial radiotherapy.

The high prevalence of incidentally detected subsequent intracranial neoplasms after cranial radiation therapy (CRT) in long-term survivors of childhood cancer and the minimal symptoms reported by those with intracranial tumours indicate that brain MRI screening of long-term survivors who received CRT may be warranted (Sabin [2014](#)).

Lee & Wernicke ([2016](#)) reviewed 14 studies in children, which reported that cranial radiation confers a 7- to 10-fold increase in subsequent CNS tumours.

An increased risk of secondary cancers and cardiovascular disease up to 20 years later was found in survivors of childhood Wilms tumour (Castellino [2011](#), Termuhlen [2011](#)). Bhatia found the risk was higher in those treated between the ages of 10 and 16. Reulen ([2011](#)) found an excess risk associated with subsequent cancers in patients older than 40 years was for digestive and genitourinary neoplasms. Also indicated were risks of developing CNS tumours, nonmelanoma

skin cancers and bone and breast cancer. Melanomas are most frequently observed after Hodgkin disease, hereditary retinoblastoma, soft tissue sarcoma and gonadal tumours, but are only in 0.14% of all childhood cancer survivors (Braam [2012](#)).

However, melanoma was found in two children after treatment for astrocytoma in a study by Frigerio ([2014](#)). The study author suggested that melanoma should be considered in the monitoring of pigmented lesions in young cancer patients.

Some develop a different form of leukaemia following treatment for T-ALL (Szczepanski [2011](#)). Szczepanski found that germline genetic abnormalities might contribute to a susceptibility to develop T-ALL.

Pettorini ([2008](#)) suggests that the infantile brain has a specific vulnerability, compared with adults. Children are more likely to develop radiation-induced cerebral tumours within 8 years of central nervous system irradiation. Radiation-induced tumours are correlated with higher levels of brain irradiation, over 80% at some distance from the maximum irradiation field. Nearly 74% were adult at the time of diagnosis of the radiation-induced tumour and 75% within 18 years after irradiation (Vinchon [2011](#)). Risks of radiation-related cancer are greatest for those exposed early in life, and these risks appear to persist through life (Kleinerman [2006](#)).

Kleinerman suggests that childhood cancer patients with inherited cancer syndromes, such as retinoblastoma, neurofibromatosis type 1, Li-Fraumeni syndrome and naevoid basal cell carcinoma syndrome are at substantial risk of developing radiation-related second and third cancers ([2009](#)). Tahasildar ([2011](#)) found that 98% of second malignancies in hereditary retinoblastomas are patients who have been treated for a bilateral disease.

Weis ([2011](#)) suggests that modulation of RAD9A and other cell cycle arrest and DNA repair proteins contribute to the risk of developing a second malignancy in childhood cancer patients.

Berger ([2011](#)) found that the risk of secondary cancers was highest after retinoblastomas, Hodgkin lymphomas, leukaemias (especially parotid gland tumours (Tugcu [2012](#))), soft tissue sarcomas, CNS tumours and bone tumours. The authors felt that the follow-up time was too short to determine whether there were an increased risk of breast cancer (median follow-up time 9.8 years). Cancer is highly prevalent among patients with paediatric end-stage renal disease (ESRD) after 25.3 years of transplantation, with a high rate of recurrence (Ploos van Amstel [2015](#)).

Osteosarcoma as second malignancy occurred 14.6 years after the first childhood cancer on average. The prognosis of osteosarcoma as second malignancy of childhood cancers may be more favourable than that of conventional osteosarcoma (Yonemoto [2015](#)).

The cumulative incidence of secondary cancers in Hong Kong (Sun [2011](#)) was comparable to western countries. Radiotherapy was associated with secondary solid tumours among patients with acute lymphoblastic leukaemia. Patients who developed a secondary brain tumour or osteosarcoma had a poor outcome.

Children who survived a non-central nervous system solid cancer have a large increased risk of developing a new malignancy, even many years after their initial diagnosis (Maule [2011](#)).

Patients with rhabdomyosarcoma (RMS) who complete therapy typically undergo 4 years of surveillance imaging despite lack of evidence that this improves outcomes. Lin ([2015](#)) compared overall survival (OS) between patients in whom progression or relapse was detected by routine clinical evaluation or by imaging. The authors felt that reduced imaging tailored to the risk and

pattern of recurrence, associated risks and cost could improve patient quality of life and decrease health-care expenditure without compromising outcome.

Cardiovascular problems

Survivors of childhood cancer should be monitored for the development of cardiac problems (Mulrooney [2009](#), Brouwer [2011](#), Basar [2014](#)). Real-time 3-dimensional echocardiography (RT-3DE) seems to detect more abnormalities in cardiac function than conventional echocardiography following childhood cancer therapy (Ylänen [2014](#)). The cumulative incidence of adverse cardiac outcomes in cancer survivors continued to increase up to 30 years after diagnosis (Goldberg [2012](#)), did not reduce over time (Kero [2015](#)) and cardiovascular disease is the leading noncancer cause of death among survivors of childhood cancer (Dietz [2014](#)). Survivors have a high and variable risk for developing an abnormal level of cholesterol or fat in the blood, and obesity, depending on cancer diagnosis and treatments (Felicetti [2014](#)).

Survivors had significantly elevated hazard ratios for cardiomyopathy/cardiac insufficiency; arteriosclerosis/brain vascular thrombosis; myocardial infarction/cardiac ischemia and cardiac arrhythmia. The risk was highest among lymphoma, brain tumour, leukaemia and testicular malignancy survivors (Kero [2014](#)).

Cardiotoxicity is increased by chemotherapy especially in older girls. Impaired artery flow is a risk following ALL treatment (Dengel [2008](#)). It is unclear whether this relates to early development of cardiovascular disease. Cardiac side effects may progress over time and are a concern for patients treated during childhood. Most cardiovascular risk statistics and clinical experience are derived from patients treated before 1985, the modern radiation approach that limits the exposure of the heart and reduces the total dose seems to attenuate the previously observed cardiovascular risk (Yahalom & Portlock [2011](#)), though Tukenova ([2010](#)) confirmed a significant excess risk of cardiac mortality that was associated with a high cumulative dose of anthracyclines. Kremer ([2001](#)) suggested that up to 5% of patients will develop anthracycline-induced heart failure up to 15 years after treatment and Lipshultz ([2014](#), [2014b](#)) concluded that anthracycline-related cardiotoxicity remains the leading cause of morbidity and mortality in survivors of childhood cancer. WA Smith ([2013](#)) found that exercise training improved exercise capacity of survivors with subclinical cardiomyopathy after anthracycline treatment.

Cardiac abnormalities were persistent and progressive after doxorubicin therapy. The problems were worst after highest cumulative doses of doxorubicin, but appeared even after low doses (Lipshultz [2005](#)).

Cardiovascular complications are the second leading cause of late mortality in survivors of Hodgkin's lymphoma (Poulin [2011](#)). Vigorous exercise was associated with a lower risk of cardiovascular problems in survivors of HL (Jones [2014](#)) and in childhood cancer survivors generally (Slater [2015](#)).

Childhood cancer survivors (who have had exposure to platinum, CRT or steroids) are more insulin resistant and have higher levels of several cardiovascular risk factors even while still children (KS Baker [2013](#)). Hypertension after radiotherapy, including cranial radiation therapy, significantly increased the risk for coronary artery disease, heart failure, valvular disease and arrhythmia (Armstrong [2013](#)), through blood pressure and weight changes (Veringa [2012](#)). Hummel ([2014](#)) found that cranial radiation therapy is associated with smaller cardiac volumes and reduced systolic and diastolic LV function.

A study by Ruble ([2015](#)) revealed that even among survivors who are comparable to their healthy siblings in other traditional cardiovascular risks, there is evidence of poorer vascular health.

Cardiovascular disease was associated in both adolescent-young adult survivors of cancer and also their siblings as a result of the cumulative impact of responses to chronic stress on interrelated organ systems and risk for stress-related diseases (Santacroce & Crandell [2014](#)).

Dental late effects

Childhood cancer therapy may impact tooth development, salivary function, craniofacial development, and temporomandibular joint function placing some childhood cancer survivors at an increased risk for poor oral and dental health. Additionally, head and neck radiation and hematopoietic stem cell transplantation increase the risk of subsequent malignant neoplasms in the oral cavity. Survivors require routine dental care to evaluate for potential side effects and initiate early treatment (Effinger [2014](#)).

Survivors of childhood cancer are at risk for dental complications as a result of both radiotherapy and chemotherapy treatments (Gawade [2014](#)). Cancer therapy may increase the risk of development of dental abnormalities, especially in children treated under the age of 5 years (Bagattoni [2014](#), Proc [2016](#)).

Depression

Young adult female survivors of childhood cancer had more depressive symptoms than their peers with no history of cancer (Cantrell & Posner [2014](#)).

Employment prospects

Physical problems may cause much of the health-related unemployment among childhood cancer survivors. Whereas both male and female survivors with neurocognitive deficits – primarily in task efficiencies – are at risk for unemployment, employed female survivors with neurocognitive deficits may face poor occupational outcomes more often than males (Kirchhoff [2011](#)).

The unemployment rate was 15.9% among childhood cancer survivors, excluding homemakers and students. Approximately 70% of unemployed survivors had some late effects, dropped out of school or had had brain tumours (Ishida [2014](#)).

Epilepsy

Epilepsy is considered the most important risk factor for long-term disability in survivors of brain tumours (Maschio [2014](#)).

Retaining fertility

As survival rates from childhood cancer increase, fertility preservation is becoming increasingly important. Ovarian tissue cryopreservation (OTC) is likely to become a viable option for preadolescent cancer patients. As research progresses, physicians must be aware of the current state of OTC, as well as ethical concerns, risks, and benefits of OTC as a fertility preserving option (Bellew [2012](#), Long [2016](#)). Discussion and action surrounding fertility preservation for adolescent and young adult patients with cancer are associated with medical factors, patient socioeconomic data, and child-rearing status. These results highlight the need for insurance coverage for fertility preservation and increased awareness of fertility preservation options (Shnorhavorian [2015](#), Benedict [2016](#)).

Fertility is decreased among female Childhood Cancer Survivor Study (CCSS) participants (Green [2009](#), [2011](#)), though new approaches are being developed to preserve fertility with different methods to restore ovarian function (Hancke [2011](#)). Woodruff ([2013](#)) says it is a challenge to identify which patients will be left infertile by cancer treatment and who might be able to conceive.

Survivors had an increased risk of clinical infertility, up to the age of 40 (Barton [2013](#)). They were less likely to be prescribed drugs for treatment of infertility. Increasing doses of uterine radiation and alkylating agent chemotherapy were strongly associated with infertility. However, 64% of those with self-reported clinical infertility achieved a pregnancy. Fertility related concerns were reported by nearly half of the participants in a study by Ellis ([2016](#)). Themes included: distress regarding potential infertility, the effect of infertility on future relationships and self-esteem; and miscommunications/confusion about fertility status, access to fertility testing and preservation options. Parents also reported challenges regarding how and when it was developmentally appropriate to talk to their children about fertility.

Females who receive treatment that depletes their ovarian reserve should be evaluated for the development of premature menopause following their treatment (Levine [2011](#)). Measurement of Anti-Müllerian hormone (AMH) can reveal apparent depletion of ovarian reserve in female childhood cancer survivors reporting normal menstrual cycles, which may thereby allow appropriate fertility counselling (Charpentier [2014](#)).

Signs of fertility impairment were observed at variable time points between 1 and 12 years after chemoradiotherapy for childhood brain tumours. People's chance of recovery from fertility impairment was increased with time since diagnosis (Pfitzer [2014](#)).

Testicular damage occurred in young male mice treated with Bortezomib, used in childhood cancer treatments. Although it seemed to have long-term effects on testicular function, the mice remained fertile and their offspring looked healthy (Hou [2014](#)). Sperm concentration was reduced in male survivors of childhood cancer who had received some chemotherapy treatments, but not radiation therapy (Green [2014](#)).

Former patients expressed moderate to high anxiety for the health of any children they may have, particularly cancer (74%) and other diseases as well (20%) (Balcerek [2015](#)).

Breastfeeding

Whilst breastfeeding has been associated with a reduced risk of childhood cancer, the few available studies report a high rate of lactation failure in women who were treated with cranial radiation therapy for childhood cancer. Breastfeeding may ameliorate some of the adverse effects of cranial radiation therapy, but a balance must be struck in the advice given between encouraging women to breastfeed and preparing them for the possibility that they may be unable to do so (Hall & McGuire [2014](#)).

Gastrointestinal problems

As well as the risk secondary gastrointestinal cancers, childhood cancer survivors may also develop gastrointestinal polyposis after radiotherapy and chemotherapy (Yurgelun [2014](#)).

Growth/height problems

Reduced height is one of the most reported consequences of cancer treatment, especially brain tumours, depending on gender, age, and place needing treatment (Gurney [2003](#), Perkins [2007](#),

Breene [2011](#)). Final height was significantly lower in children receiving an allogeneic stem cell transplantation before the age of 5 (Freycon [2012](#)). Growth hormone (GH) treatment had only a modest effect on growth velocity. Early GH treatment and analysis of serum IGF-1 were thought to be helpful for improving final height or growth outcome (Chae [2013](#)). Body mass index (BMI) was normal, but decreased in boys treated with fractionated total body irradiation (fTBI).

Growth hormone secretion after conformal radiation therapy (CRT) can be predicted on the basis of dose and time after irradiation in paediatric patients with localised brain tumours. The results of the study by Merchant ([2011](#)) provide an objective radiation dose constraint for the hypothalamus. Obesity risk is increased for paediatric central nervous system tumour survivors. Hypothalamic involvement (HI) by tumour or treatment increases the risk (Strobel [2016](#)).

Pituitary deficits are common after CRT. Continued development over time is noted for growth hormone and other hormone deficiencies (GHD, and LH/FSHD) with possible associations between nontreatment of these conditions and poor health outcomes (Chemaitilly [2015](#)).

25 years after diagnosis, ALL patients that were growth deficient experienced a significant decrease in Z-scores possibly suggesting a premature risk for osteoporosis. Growth hormone therapy was not shown to have a clear beneficial effect on bone mineral density, possibly the normal dose may be too low (Follin [2011](#)), though it did achieve heights within the 'normal' range for some of the children, especially girls (Isfan [2011](#)). GHRT carried no risk of recurrent neoplasms in a study by Mackenzie ([2011](#)), thus supporting the treatment following CNS radiation. There was a slight, but non-significant risk of CNS neoplasms associated with GH treatment (Patterson [2014](#)).

A decline of bone density occurs from the moment of osteonecrosis diagnosis, which suggests that bone density decline has begun to occur during acute lymphoblastic leukaemia therapy. It is further aggravated by factors such as restriction of weight bearing activities. Therefore osteonecrosis can be considered as a risk factor for low bone density in children with acute lymphoblastic leukaemia (den Hoed [2015](#)).

Growth hormone therapy for 2 years in young adult survivors of childhood ALL, including total body BMD and lean mass were significantly higher whereas the percentage fat was significantly lower. Several psychological measures also improved (van den Heijkant [2011](#)).

Family support

Latino survivors' experiences demonstrate that they simultaneously face uncertainty and identify positive influences of the cancer experience in particular unwavering familial support. They need borrowed strength of family and hospital staff; sustained positive attitude; and they have perceived vulnerability; and can be branded a cancer survivor (Phillips & Jones [2014](#)).

Infections

Survivors of childhood cancer remain at elevated risk for developing infectious-related complications, and they have a higher risk of infection-related mortality years after therapy (Perkins [2014](#)).

An important life-threatening complication of intensive chemotherapy administered in children with leukaemia is febrile neutropenia. Özdemir ([2016](#)) reported that the patients treated in a centre in Turkey after year 2000 had statistically significantly more febrile neutropenia attacks compared to the patients treated before year 2000. The increments in treatment intensities seemed to increase the incidence of febrile neutropenia while improving survival.

Metabolic syndrome

Skoczeń (2011) suggested that childhood ALL survivors should be screened for markers of the metabolic syndrome which the team had identified. These were risk factors for obesity and diastolic hypertension, among other things, especially in girls.

Patients treated with haematopoietic stem cell transplantation (HSCT) may develop insulin resistance early after transplantation. They do not show overt obesity, but have redistribution of fat tissue with central fat accumulation. The main factors associated with increased metabolic risk are total body irradiation and time from HSCT. Evaluation of metabolic syndrome and glucose tolerance should be part of hormonal follow-up, which should be routinely proposed to these patients (Bizzarri 2015).

Paediatric brain tumour survivors following radiation therapy should be monitored for the diagnosis of metabolic syndrome traits predisposing to cardiovascular disease (Siviero-Miachon 2011).

Experience of pain

37% of paediatric brain tumour survivors had clinically significant pain (Chordas 2013).

Physical activity

Interventions designed to maximize physical activity should target female, obese, and less educated survivors. Survivors with chronic musculoskeletal conditions should be monitored, counselled and/or referred for physical therapy. Clinicians should be aware of low activity levels among sub-populations of childhood cancer survivors which may heighten their risk for chronic illness (Wilson 2014). Wada (2013) found that 44% of multi-ethnic cancer survivors in Hawaii less than 18 years old and 29% of those aged 18 or more failed to meet national guidelines for physical activity recommendations; and they had a low intake of fruits and vegetables, making them at higher risk of chronic disease. Zhang (2014) found that energy expenditure by the studied childhood cancer survivors was about 4/5 of the recommended levels, which would contribute towards obesity risk.

Physical activity has been targeted as a health promotion priority in child and adolescent cancer survivors, though a large proportion do not meet the recommended levels of activity (Gilliam & Schwebel 2013). Lam (2017) discovered that the patients' physical condition, misunderstanding about physical activity by children, parents and healthcare professionals, emotional disturbances and social influences are four important factors impeding children from engaging in regular physical activity during cancer treatment. Understanding these factors, nurses can explore interventions that target on correcting the misunderstanding and providing relevant information about the importance of physical activity.

Muscle strength and balance seem to be impaired in varying degrees in childhood cancer survivors depending on the diagnosis, treatment received, and time elapsed between treatment and evaluation. Individual targeted exercise therapy programs during treatment and follow-up of childhood cancer could help to prevent and further diminish impairments of muscle strength and balance function (Söntgerath & Eckert 2015). Percentage of patients or survivors in the impaired range of balance varied between 27-69% during treatment, 7-65% a few years after completion of treatment and 14-17% many years after the completion of treatment (Varedi 2017).

Psychosocial difficulties

A study by Takei (2014) suggested that early signs of difficulties should be watched for and early support offered. Cancer survivors expressed concerns about physical, interpersonal and behavioural difficulties and uncertainty about the future.

Acute leukoencephalopathy during chemotherapy treatment, without cranial radiation, for childhood acute lymphoblastic leukaemia predicted higher risk for long-term neurobehavioural problems and reduced white matter integrity in frontal brain regions. Survivors of childhood acute lymphoblastic leukaemia might benefit from preventive cognitive or behavioural interventions, particularly those who develop acute leukoencephalopathy (Cheung 2016).

Children surviving cancer had more emotional symptoms, higher total problem scores and poorer academic performance than their peers. Emotional problems were consistently reported by parents, teachers and adolescents themselves, in particular in children with brain tumours and among survivors with late effects. They are at higher risk for emotional problems when compared with their friends, even after several years following diagnosis and treatment. We conclude that when planning long-term follow-up care, rehabilitation of children and adolescents with cancer, especially for survivors with brain tumours and late effects, should particularly take into account their psychological problems and psychosocial functioning (Eilertsen 2011).

Interventions to improve the social competence of brain tumour survivors and classmates were undertaken in a US school. There were 5-8 sessions over 4-6 weeks. Preliminary outcome data trended toward some benefit in increasing the number of friend nominations for survivors of brain tumours but no changes in other peer-reported metrics. Preliminary results also suggested some positive effects on classroom levels of victimization and rejection (Devine 2016).

Pulmonary weakness

Only 37% of adult paediatric cancer survivors and a dramatically low 6% of non-Hispanic black survivors had an influenza vaccination in 2009. This is despite the fact that a large proportion of long-term survivors of childhood cancer have treatment-related adverse cardiac and pulmonary late-effects, with related mortality. Consequently, this population of approximately 379,000 individuals in the U.S. is at high risk of complications from influenza infections (Ojha 2014).

Pulmonary complications are frequently seen in survivors of childhood cancer, and are due to both disease-related and treatment-related causes. While primary lung cancer is extremely rare in the paediatric population, the lung is a common site for metastatic disease. Therapies used to treat the paediatric population can cause long-term damage to the sensitive lung tissue (Josephson & Goldfarb 2014).

Treatments for childhood cancer can impair pulmonary function (Mulder 2011). Oancea (2014) suggested that childhood cancer survivors have an increased risk for obstructive and restrictive lung disease and that follow-up is needed to determine if smoking imparts more than an additive risk. They felt that smoking prevention and cessation need to be a priority.

Sex and reproductive effects

29% of young adult cancer survivors reported 2 or more discrete symptoms of sexual dysfunction, unrelated to specific types of childhood cancer treatment. Females were twice as likely to report sexual problems (Bober 2013). Survivors reported significantly lower sexual functioning, lower sexual interest, lower sexual desire, lower sexual arousal, lower sexual satisfaction, and lower sexual activity compared with siblings (Ford J 2014). Risk factors for

poorer psychosexual functioning among survivors included older age at assessment, ovarian failure at a younger age, treatment with cranial radiation, and cancer diagnosis during adolescence.

For childhood cancer survivors who maintain fertility, health risks to offspring resulting from their cancer treatment are major concerns. Radiation affecting ovarian and uterine function has been linked to pregnancy complications, including spontaneous abortion, preterm labour, foetal malposition and low birth weight. The risk of congenital malformations, genetic disorders and cancer appears to be low (Signorello [2011](#)), with the exception of cancer risk in offspring born to survivors with germline cancer-predisposing mutations (Hudson [2010](#)). Mueller ([2009](#)) found that infants born to female survivors of childhood and adolescent cancer were not at increased risk of malformations or death. Increased occurrence of preterm delivery and low birth weight suggest that close monitoring is warranted.

Peasant ([2016](#)) suggested that it would be helpful if health care providers might take on the role of advocates for mother-daughter sexual communication and HPV vaccination among survivors of childhood cancer.

Sleep problems

Children and adolescents with cancer have fatigue and sleep problems at home that vary by age, gender, and cancer diagnosis. The cancer survivors report insomnia, associated with poor physical health and anxiety. Few of them discuss this issue with oncology care providers (Zhou & Recklitis [2014](#)). Data from the study by Darezzo Rodrigues Nunes ([2015](#)) supports the need for nurses to provide teaching about fatigue and sleep at home. While survivors reported achieving recommended amounts of sleep each night, 20 to 30 % reported excessive daytime sleepiness in a study by Brimeyer ([2016](#)).

Substance use

Young adult childhood cancer survivors and non-Hispanic white survivors are at greatest risk for developing substance use behaviours. The frequency of substance use among adolescent and young adult survivors appears to increase as they transition into adulthood (Ruiz [2016](#)). These findings emphasize the need to improve long-term health behaviour screening and develop effective interventions on reducing substance use behaviours in this vulnerable population.

Taste dysfunction and dietary preferences

Reduced or altered taste may occur as a side-effect of cancer therapy. This dysfunction can persist many years after treatment completion. Taste dysfunction was found in 27.5% of study participants (Cohen [2014](#)). The child cancer survivors' appeared to 'like' the less healthy food groups such as flavoured drinks, takeaway and snacks over healthier food groups such as vegetables and salad (Cohen [2015](#)). Maybe this taste dysfunction plays a role in the dietary habits and therefore potential weight problems (see below). It is worth persisting as current research seems to indicate that a diet high in vegetables, and to a lesser extent fruit, significantly reduces risks to health (Wise [2014](#)).

Cancer patients should be counselled on the potential impact taste and smell dysfunction can have on their appetite and oral intake (Cohen [2016](#)).

Total body irradiation (TBI)

TBI is still the most effective form of treatment for many paediatric malignancies. However, a significant number of cancer survivors go on to develop secondary malignancies following this treatment (Linsenmeier [2010](#), Kotecha [2011](#)). Bresters ([2016](#)) and a large international team of researchers reported that TBI was a risk factor for having any late effects in children under the age of 3.

In a study by Felicetti ([2011](#)), Leydig cell failure was found in 23% of patients receiving TBI and elevated FSH levels, suggesting spermatogenesis damage was found in all patients. Primary hypothyroidism was more common.

Rajendran ([2013](#)) found children who had received TBI were at risk of diabetes and an exaggerated form of the metabolic syndrome with hypertriglyceridaemia, which can be life-threatening. TBI was also identified as a major risk factor for metabolic syndrome (Oudin [2011](#)).

Premature musculoskeletal joint failure is a major source of morbidity among childhood cancer survivors. Late degenerative changes in articular cartilage and bone were observed after total body irradiation in adult rats exposed prior to skeletal maturity (Hutchinson [2014](#)).

Total body irradiation-associated growth hormone deficiency increases the risk of SCFE (Mostoufi-Moab [2013](#)) causing groin, knee or thigh pain, particularly in obese, adolescent black males.

Vaccinations

Fayea ([2016](#)) found that 93% of our patients were considered seronegative (unprotected) for at least one vaccine-preventable disease. These represent a subpopulation of high-risk patients who might benefit from revaccination. The authors suggested a potential revaccination approach for childhood cancer survivors, which is easily applicable and of low cost.

Weight problems

Obesity is a late effect in survivors of childhood cancer and correlates with chronic complications. Survivors of leukaemia, brain tumours, and hematopoietic stem cell transplantation are more likely to develop obesity resulting from treatment modalities such as radiotherapy and glucocorticoids. The mechanisms involved in the pathophysiology of obesity in cancer survivors are not completely understood, but it is believed that damage to the hypothalamus and endocrine disorders such as insulin resistance, leptin resistance, and hormone deficiency may be involved. The use of body mass index in these patients may lead to an underestimation of individuals' risk for metabolic complications (Teixeira [2016](#)).

Robien ([2008](#)) suggests that there is a poor adherence to dietary guidelines, with too high a consumption of salt and sugar and inadequate whole grains that may be at least partially responsible for the obesity which is one of the more common after effects of treatment. CNS tumour survivors who are overweight are more likely to have complaints of excessive daytime sleepiness and are at greater risk of sleep-disordered breathing (Mandrell [2011](#)). Unhealthy body weight and overfatness was thought to be common amongst Saudi survivors of standard risk ALL, though it may not have been more common than in the general Saudi adolescent population (Aldhafiri [2011](#)). It may be that weight issues vary from country to country. Fleming ([2015](#)) and Prasad ([2015](#)) wondered whether the lower numbers of those overweight in their Australian (Fleming) and Mumbai (Prasad) studies was due to the underlying undernutrition in that

country, or whether the cohort of survivors was distinct from their Western counterparts. Those with ALL or a brain tumour were more likely to be overweight.

Children diagnosed with ALL during the preschool and school-age developmental years have the greatest vulnerability of developing obesity or being overweight. Obesity and overweight prevention efforts are greatly needed in children with ALL, and efforts should occur before ALL treatment completion in preschool and school-age children (Winkler [2015](#)).

Male CNS tumour survivors were overweight more; female survivors, who were diagnosed at age 10 and under, had a 10% higher risk of being obese than survivors diagnosed at ages 16-20 (Warner [2014](#)).

Green ([2012](#)) suggests that a variety of factors may contribute to the problem of weight. These include treatment, lifestyle and intrapersonal factors, as well as the use of specific antidepressants. Obesity is associated with gonadal dysfunction in male survivors. Weight normalisation might improve gonadal function (Blijdorp 2014).

In a study by Elchuri ([2014](#)) nearly 5% of paediatric cancer survivors were underweight, nearly 20% overweight and over 16% obese. The abnormal body mass indices, especially overweight, were not correctly perceived by survivors, their parents or providers.

Berdan ([2014](#)) suggested that there was much room for improvement in educating and encouraging survivors to follow healthier diet and lifestyle routines to prevent obesity and further morbidity.

Improved weight, weight-related behaviour, and psychological outcomes were demonstrated following Fit4Life intervention, a weight management intervention tailored for childhood ALL survivors (Huang [2014](#)).

Other physical effects

There are many other physical health problems that are consequences of childhood cancer treatment. Platinum-based therapy, including cisplatin, carboplatin, oxaliplatin or a combination of these, is used to treat a variety of paediatric malignancies. Unfortunately, one of the most important adverse effects is the occurrence of hearing loss (van As [2016](#)).

Strokes are more likely in survivors of brain tumours (Bowers [2006](#), Gurney [2003](#)). Childhood cranial radiation therapy increases the risk of stroke in survivors. Artherosclerotic risk factors enhanced this risk (Mueller [2013](#)).

One of the most reported problems is sleep-wake disturbance, leading to decreased daytime alertness, possibly due to irregular melatonin secretion, following hypothalamic injury resulting from the brain tumour and its treatment (Gapstur [2009](#)).

Hodgkin's disease survivors had more problems with fatigue and sleep, especially in young women (21-25 years). They also had lower quality of life scores (Calaminus [2014](#)). There was an increased risk of Diabetes Mellitus in Hodgkin's Lymphoma survivors (van Nimwegen [2014](#)).

Restrictive lung disease was more frequently found after stem cell transplantation in childhood cancer survivors (Frisk [2011](#)). The incidence of non-infectious interstitial lung disease (ILD) after HSCT was not negligible, and the clinical features of ILD showed late onset and a poor prognosis. Female gender and high-dose cyclophosphamide treatment may be risk factors for non-infectious ILD (Y Lee [2016](#)). Loisel's study ([2016](#)) pointed to potentially modifiable factors that are

related to the course of HRQOL following HSCT, and interventions aimed at these factors should be implemented.

Cancer survivors are twice as likely to have late-onset complications of the upper and lower gastrointestinal tracts and the liver (Goldsby [2011](#)).

Late complications occur in many CNS tumour survivors. These complications include as well as hearing loss, blindness, cataracts, double vision, hypothyroidism, seizure disorders, need for medical induction of puberty, osteoporosis, cardiovascular conditions angina-like symptoms, ovarian failure and musculoskeletal (including co-ordination and motor control) problems (Ryan & Kay [2011](#)), pulmonary abnormalities (Laverdière [2005](#), Packer [2003](#), Gurney [2003](#)) and immune system dysfunction (Ek [2011](#)). The majority of these are of mild-moderate severity, with only 4% being life-threatening (Laverdière [2005](#)). Hypothyroidism is a common finding amongst adult survivors of childhood malignancy (H Lee [2016](#)). The substantial differences in reported hypothyroidism prevalence after irradiated CNS neoplasms suggests substantial under-diagnosis (Brabant 2012).

Seizures occur in most patients with primary malignant tumours and are associated with poor quality of life. Patients with high grade brain tumours were asked about their experience of seizures (Shin [2016](#)). The theme of adaptation and acceptance-or lack therefore-to seizures emerged. With respect to this theme, some patients conveyed frustration from an inability to work, to drive, and to take care of their children. Others described frustration with taking anti-seizure medications. These findings should serve to make healthcare providers more aware of the heavy emotional burden that seizures thrust upon brain tumour patients.

Lower bone mineral density (BMD) is associated with osteoporosis or osteopenia. BMD is lower than expected in adult survivors of childhood ALL, specifically in men (Thomas [2008](#)), depending on the treatment received (Le Meignan [2011](#)). Despite continuous growth hormone therapy, low BMD was recorded in childhood onset craniopharyngioma in females. Insufficient oestrogen and androgen supplementation during adolescence was the main cause, but hypothalamic involvement with consequent leptin resistance was also strongly associated with low BMD in both genders (Holmer [2011](#)). Prolonged glucocorticoid (GC) use and reduction in body mass index (BMI) are risk factors for decreased BMD in childhood cancer survivors (Choi [2013](#)).

Bone growth defects are associated with methotrexate (Fan [2011](#)) and Imatinib mesylate (Choeprasert [2017](#)). Vitamin D supplementation may help with on height velocity and BMD in CML patients.

7% of survivors of medulloblastoma/PNETs developed low-grade bone lesions (Koral [2012](#)). Hearing and cognitive impairments are the most common toxicities as a result of craniospinal radiation treatment for medulloblastoma (Christopherson [2014](#)). One 15-year old boy who had been in remission for 10 years after a central PNET developed pheochromocytoma, normally found only in adults. It was suggested that there may have been some unidentified linkage or common genetic background (Nakano [2013](#)).

Therapeutic radiation has been associated with an increased risk for late mortality, pulmonary (Tantawy [2011](#)), cardiac and thyroid dysfunction as well as an increased overall risk for chronic health conditions (Armstrong [2010](#)). Children under 3 when treated with hematopoietic cell transplant (HCT) for ALL or AML were more likely to suffer from hypothyroidism, decreased bone mineral density, osteochondromas and dyslipidemias (increasing the risk of cardiovascular disease), & strokes (Perkins [2007](#), Gurney [2007](#)). There was an increased risk of hypothyroidism found in patients treated with a combination of chemo-and radiotherapy (Cağlar [2014](#)).

Survivors had talked more often to a doctor than the general population, had increased hospital outpatient, day-patient and inpatient visits. Survivors of Hodgkin's lymphoma, neuroblastoma

and Wilms tumour had the highest amount of day-patient care, whereas survivors of CNS tumours and bone sarcomas had the highest number of outpatient and inpatient visits. It did not vary significantly with age (Rebholz [2011](#)). McBride ([2011](#)) reports that 97% of survivors saw at least 1 doctor 3 years on, compared to 50% of the general population. The probability of a GP visit was 96% higher and a specialist visit 157% higher than for the general population. Survivors were more than twice as likely to see GPs at least 10 times and had 49% more visits than the general population.

Liver complications are common after treatment for childhood cancer. In a review of studies reporting hepatic effects, Mulder ([2011](#)) was unable to determine which part of treatment increased the risk.

Oral complications directly or indirectly associated with leukaemia treatment include mucositis, opportunistic infections, gingival inflammation and bleeding, xerostomia and carious lesions. An additional consideration in children is the impact of the treatments on the developing dentition and on orofacial growth (Valéra [2014](#)).

According to Edelstein ([2011](#)), the most common health implication in survivors of childhood medulloblastoma were hearing impairment, second cancers, diabetes, hypertension and endocrine deficiencies.

Intervention studies to date have focused on smoking cessation, diet, and exercise, as well as improving rates of late effects surveillance in childhood cancer survivors (Henderson [2014](#)).

Adolescent and young adult survivors of medulloblastoma showed centripetal fat deposition and decreased insulin sensitivity, associated with growth hormone secretion status.

Almost half of survivors of childhood leukaemia suffered from at least one effect (Pakakasama [2010](#)) in a study from Thailand.

Childhood cancer survivors, especially those who had had medulloblastoma or osteosarcoma, reported an inactive lifestyle compared with siblings. Treatments with cranial radiation or amputation were associated with an inactive lifestyle as were being a woman, black race, older age, lower educational attainment, underweight or obese status, smoking and depression (Ness [2009](#)).

12% of a sample of paediatric cancer survivors reported smoking (Roberts [2014](#)).

Pain conditions (pain/abnormal sensation, migraines and other headaches) were reported by between 12 and 21% of survivors. 17% reported use of prescription analgesics and 21% attributed pain to cancer and treatment. Younger age at diagnosis and a history of non-Hodgkin lymphoma, Wilms tumour or neuroblastoma were associated with a greater risk of reporting pain conditions. A history of bone cancer or soft tissue sarcoma was associated with greater risks of using prescription analgesics and cancer-related pain attribution. Female gender and lower educational attainment were associated with increased reports of all 3 pain outcomes; minority status, unemployment and being single were associated with greater risks for reporting pain conditions (Lu [2011](#)).

C. was diagnosed with leukaemia at the age of 13. She was sporty and rarely ill. For the next two years, she was forced to undergo regular treatments, another round of chemotherapy, more steroids and constant blood tests. The family led a surreal existence, spending most of their weekends in hospitals, cancelling all holidays and having to be scrupulous about hygiene at home because C's lowered immunity made her prone to infections. She put a lot of weight on and 8 years after diagnosis, still has a very circular face now from the steroids. To this day she says "I

look different to how I would have without cancer.” Several months after beating the cancer, she started experiencing agonising pain in her legs. She was diagnosed with Avascular Necrosis (AVN), a bone condition caused by the drugs she needed for her cancer treatment. 10 to 15 per cent of teenage girls treated for leukaemia, suffer from AVN. C. was left in constant pain. “I did really badly in my A-levels because of it,” she explains. “I was constantly spaced out on morphine. She still gets a lot of bad pain in her legs.

Neurocognitive effects

ALL survivors tested significantly lower on verbal IQ and performance IQ 20 years after diagnosis, compared with healthy young adults, especially when treatment included cranial irradiation (Harila [2009](#)). Neurologic complications were also found by Goldsby ([2010](#)) following cranial radiation for ALL. Anderson ([2008](#), [2009](#)) found a link between white brain matter damage and some of the more subtle neurocognitive late effects, such as difficulties with thinking and reasoning. The higher the dose of radiation and chemotherapy, and the younger the age at treatment, the more neurocognitive effects are likely (Edelstein [2011](#), Kesler [2014](#)) especially evident on tasks involving rapid processing of information. Neurocognitive sequelae are known to be induced by cranial radiotherapy and central-nervous-system-directed chemotherapy in childhood Acute Lymphoblastic Leukaemia (ALL) and brain tumour patients. Sleurs’ study ([2016](#)) highlighted a need for neurodevelopmental focused research in children who are treated for solid non-CNS tumours, since they are at risk for potential neurocognitive impairment.

Children treated with radiation performed less well than those who did not receive radiation, suggesting difficulties with more basic processes such as vigilance (Raghubar [2016](#)), affecting working memory, processing speed, and attention which have been identified as problematic.

Intrinsic functional brain connectivity is disrupted in paediatric ALL following chemotherapy treatment. These results help explain cognitive dysfunction. Children diagnosed at a younger age results in significantly less cerebral white matter volumes (WMV) than their peers and this difference increases with time since therapy. Decreased WMV is associated with significantly lower scores in intelligence, attention and academic performance. Brain tumour survivors were more affected than ALL survivors (Reddick [2014](#)).

Parents of brain tumour survivors report more psychosocial and executive problems in their child than other parents. Teachers indicated more psychosocial adjustment problems for girls aged 8-11 years (de Ruiter [2015](#)). The effects of surviving brain cancer affect the entire family unit. A need for support is evident, although the development of such support necessitates a more full understanding of challenges face by the child affected, their parents, and siblings (Woodgate [2015](#)). De Ruiter ([2015](#)) recommended systematic screening of psychosocial functioning so that tailored support from professionals can be offered to paediatric brain tumour survivors with neurocognitive complaints. Children with a brain tumour are at risk for a number of physical and cognitive problems that may lower their health-related quality of life. Deficits in executive functioning and intellectual ability may be amenable to interventions (Netson [2016](#)).

As paediatric brain tumour survivors may experience cognitive decline post-treatment, a neuropsychology assessment and report are often produced. The majority of parents and teachers had a sound understanding of the report (Cheung [2014](#)). Implementation of recommendations at home and school was 47% and 41%, respectively. Recommendations that did not require extra effort and organization appeared more likely to be implemented, however, those perceived to be more effective or helpful did not necessarily have higher implementation rates. Key reported barriers to implementation barrier were patient reluctance, and a lack of parents' willingness to adopt the recommendation.

Memory differences between survivors and controls seem to be related to hippocampal volume which was found to be significantly lower for survivors (Jayakar [2015](#)).

Educational outcomes

More survivors had compulsory age schooling only and fewer acquired a university degree (Kuehni [2011](#)). Survivors of CNS tumours, or those who had suffered a relapse, had poorer outcomes. Central nervous system-directed therapy is associated with specific neurocognitive problems. Visual-spatial skills and verbal and visual short-term memory predict academic outcomes (Moore [2016](#)). Early assessment of visual-spatial perception and short-term memory can identify children at risk of academic problems. Children who are at risk of academic problems could benefit from a school-based individual educational program and/or educational intervention.

Psychological and Social Effects

The experience revealed by children, adolescents and young adults, survivors of cancer, showed that they feel the impact of late effects in their lives (Whitaker [2013](#)).

Childhood cancer survivors, both with and without benefits, reported lower scale scores with respect to social and psychosexual development (Maurice-Stam [2013](#)). A significant number of childhood cancer survivors had low self-esteem and experienced high levels of depression. The study (Li [2012](#)) also indicated that greater symptoms of depression in childhood cancer survivors were associated with a higher state of anxiety, lower self-esteem and poor quality of life.

During adolescence, survivors demonstrated higher rates of attention deficits, emotional problems, externalising behaviour and social withdrawal. These psychological problems are associated with an increased risk for obesity and poor health behaviour in adulthood (Krull [2010](#)). 23 % of children who survived ALL show maladaptive trajectories of internalizing behavioural problems and/or externalizing behavioural problems (Sint Nicolaas [2016](#)).

Childhood brain tumour survivors may possess the social knowledge required for social situations, but have difficulty enacting the required behaviour (Schulte [2014](#)).

Childhood cancer survivors in Switzerland reported consuming alcohol more frequently and to engage in binge drinking more than the control group (Rebholz 2012).

Survivors of childhood chronic illness, including cancer, had lower odds of graduating from college, being employed, and had higher odds of receiving benefits, and lower mean income. They had similar odds of marriage, having children, living with parents and romantic relationship quality (Maslow [2011](#)). Pillon ([2013](#)) found that long term survivors receiving cranial radiotherapy as central nervous system treatment for acute lymphoblastic leukaemia (ALL) had similar employment rates to those of controls, but lower marriage rates. A new website has been set up to improve the prospects of finding a life partner for young people in India who have had cancer. As well as bringing together former patients the website will arrange counselling for users about their medical history and the impact it will have on their future (Bagchi [2014](#)).

Adolescent survivors of childhood cancer reported lower social self-efficacy (Foster [2014](#)).

Public stigma is a major source of stress for cancer survivors. Higher levels of perceived public stigma predicted higher levels of internalized shame and self-blame and lower levels of social support availability, which subsequently increased psychological distress (Kim & Yi [2014](#)).

The self-image of many childhood cancer survivors deteriorates and they are socially isolated. Social and moral support can bring positive emotional development and helps to correct their self-perception (Sadruddin & Hameed-Ur-Rehman [2013](#)). It is important to follow a programme of psychological screening in the follow-up of childhood cancer survivors, and to address the needs of siblings. 34% of survivors and 24% siblings used mental health care provision (Gianinazzi [2014](#)).

Parental experience (see also Section 10)

35% of survivors and 29% of their parents reported severe levels of posttraumatic stress symptoms PTSS (Bruce [2011](#)). The death of a child, the parent's perception of child psychological distress and total symptom burden predicted higher levels of PTSS, as did being unemployed or having immigrant status (Lindahl Norberg [2012](#)).

Quality of life (QOL)

Fakhry ([2013](#)) found that demographic differences, cancer types, and treatment regimens all significantly influence the negative impact of cancer on children and adolescents' health-related quality of life.

Long-term neuroblastoma survivors, especially those with hearing loss, are at greater risk of having academic learning problems and psychosocial difficulties. This is reflected in the child reporting loss of quality of life, due to the stress this causes (Gurney [2007](#)). Cancer-related pain was associated with elevated distress. Survivors who reported moderate learning or memory problems were more likely to have elevated distress than survivors who reported no learning or memory problems (Oancea [2014](#)).

Adult survivors report that emotional well being continues to be affected into adult life (Nathan [2007](#)), though Zebrack ([2004](#)) found the levels of psychological stress very similar to that of the general population. Certainly Lemétayer ([2016](#)) found that most of the daily difficulties perceived by school-age children in remission from cancer had short-term effects. The study authors conclude that the difficulties encountered by children in remission from cancer are not necessarily cumulative over time and that they do not inevitably result in permanent psychological suffering.

Mört ([2010](#)) found that the diagnosis of Wilms tumour or neuroblastoma may carry substantial risks for a lower quality of life compared with those with a diagnosis of leukaemia.

Craniospinal irradiation and chemotherapy for brain tumours were negatively correlated with health-related QoL (Kuhlthau [2012](#)), assessed both during radiation and annually thereafter.

Adult survivors of cancer with onset during adolescence experience less life satisfaction than the general population, and are less likely to live independently (Kunin-Batson [2011](#)). The problems include psychological distress, somatic late effects and a lack of posttraumatic growth (Seitz [2011](#)), and in another study included anxiety and depression as well (Seitz [2010](#)). Ness ([2008](#)) reported that those survivors of childhood cancer who were worse affected were less likely to be employed, married, or have incomes greater than \$20,000 a year. They were also likely to have problems getting health insurance. Emotional health limitations had the most impact.

The prevalence of post-traumatic stress disorder in young adult survivors of childhood cancer ranges from 6 to 22%; associated risk factors are young age at the assessment, female gender, low education level, and some disease-related factors (Tremolada [2016](#)). Their study suggested that female gender and less perceived social support were significant risk factors to developing post-traumatic stress symptoms (PTSSs).

Areas of agreement and disagreement are both important to consider when examining self-reports by parent-proxy and child. There was poor agreement between parent-proxy and sibling's self-reports, particularly on social and emotional subscales. The findings from this study have important implications for future research and suggest that the impact of cancer on siblings should be further investigated (Schulte [2016](#)).

However, some studies have shown high health-related quality of life (HRQoL) scores in childhood survivors, at least as high as their siblings, when treated only with chemotherapy (Molgaard-Hansen [2011](#)) and reduced indices of depression, especially those with more severe late effects and intensive therapy (Harila [2010](#), [2011](#)). Perhaps pre-morbid personality differences play a part, or possibly support and after-care services available to patients, families and carers.

Hudson ([2003](#)) found that adult survivors of childhood CNS tumours were likely to report problems with adverse general health, mental health, activity limitations and functional impairment. The impact is aggravated by perceived shortcomings of long-term follow-up (Hovén [2013](#)).

Survivors of childhood brain tumours were at risk of impaired health-related QoL in 'physical wellbeing', 'moods and emotions', 'peers and social support' and 'bullying'. Those who had adjuvant therapy as well as surgery also had low scores for 'psychological wellbeing' (Aukema [2013](#)).

Survivors do experience lower level of QoL and psychological factors, especially self-concept, was reported in a study from Korea (Rhee [2014](#)).

Central nervous system cancer survivors scored less well with respect to physical well-being, social support and peer-group measures. Female survivors of all tumours had lower scores for physical and psychological well-being, social support and peers, parent relations, home life, school environment and autonomy. Scores decreased with length of time from diagnosis (Pérez-Campdepadrós [2014](#)).

Physical exercise and productive coping were related to higher health-related QoL in a study by Castellano ([2013](#)). The studies that included direct parental involvement showed positive outcomes on a variety of measures suggesting that increasing parental involvement in interventions for CCS may be one way to promote long-term lifestyle changes for paediatric cancer patients (Raber [2016](#)). Survivors of childhood onset lower-extremity sarcoma are highly likely to be physically inactive, especially if female (Wampler [2012](#)).

Cancer survivors showed a higher global plasma cortisol level as well as higher amplitude in the response to an experimental stress test. This global cortisol level was increased when depression symptoms were present (Laufer [2011](#)).

Endocrine conditions were found in 57% of survivors (Patterson [2011](#)) or more (30 endocrine disorders in 26 women) (Sánchez González [2016](#)), and in over 40% of survivors aged 60 or more. (de Fine Licht [2014](#)). The commonest types were weight and gonadal function (van Dorp [2012](#)). Stem cell transplant, radiation and older age at cancer diagnosis were associated with higher risk of an endocrine condition. Radiation, stem cell transplant and sarcoma diagnosis were associated with growth problems.

The percentage of children who have had stem cell transplantation who subsequently have physical disabilities vary from 7% to 17% in studies where the outcome was based on clinician or self-report measures, to over 40% in studies where the outcome was based on a directly measured physical performance task (Parsons [2012](#)). Little data on outcomes beyond 5 years post-transplant have been obtained.

Some of the endocrine effects found by Kuperman (2010) were short stature, precocious puberty, thyroid diseases, obesity and diabetes.

Survivors scored significantly lower than siblings in physical function, role limitation, and general health. These were associated with a diagnosis of CNS tumour, retinoblastoma or bone tumour, having had surgery, crano-spinal irradiation or bone marrow transplantation. Lower score in Mental Component Summary was associated with older age. All health problems decreased HRQoL in all scales. Most affected were survivors reporting memory problems and musculoskeletal or neurological problems. Health problems had the biggest impact on physical functioning, general health, and energy and vitality (Rueegg 2013).

Parents reported problems in social functioning and isolation related to a delay in emotional development. Children surviving brain tumour treatment have a reduced quality of life. The authors therefore recommend regular screening of HRQoL and emotional and behavioural problems and referral to specific aftercare (Dessens 2016).

Sexual Behaviour

Risky sexual behaviour in adolescents surviving childhood cancer is associated with cancer type, time since diagnosis, psychological health, alcohol use and peer influences (Klosky 2014).

Siblings

Siblings of long-term childhood cancer survivors are psychologically healthy in general. There are, however, small subgroups of siblings at risk for long-term psychological impairment (Buchbinder 2011).