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To the childhood and young adult cancer survivors

ABSTRACT

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Psychosocial outcomes after young age onset cancer

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Annales Universitatis Turkuensis, Medica-Odontologica, Turku, Finland, 2018

Background: Since the number of childhood and adolescent/young adult (AYA) cancer survivors is increasing due to improved survival rates, the incidence of cancer associated late-effects has also increased. Cancer survivors need to receive structured and supportive follow-up.

Aims and methods: In order to reveal the psychosocial outcomes of childhood and AYA cancer survivors, four national, registry-based studies were conducted. In the first study, educational and social outcomes of childhood cancer survivors were examined in comparison with age-matched population controls. The following study aimed to determine, whether the modifications made to the acceptance guidelines of military service have altered childhood cancer survivors' enlistment rates, and how well the enlisted survivors perform in the physical fitness and cognitive tests as compared to healthy controls. In two studies, psychiatric outcomes of childhood and young adult cancer patients were examined by assessing Hospital Discharge Register and Drug Purchase Register to determine late psychiatric morbidity as well as and frequencies of antidepressant purchases by cancer patients as compared to siblings.

Results: There was an elevated proportion of survivors with no further education after comprehensive school in all three main diagnostic groups (brain tumors (BT), solid tumors (ST), leukemias/non-Hodgkin lymphomas (NHL). However, the risk for unemployment was not increased, but early retirement was more common in comparison to the general population. The exemption rate from military service of cancer survivors was found to be significantly higher than that of population controls, but in general terms, the enlisted survivors coped well with their military training. It was found in study III that, the risk for organic memory/brain disorder was higher in cancer survivors in both age groups (0-19 and 20-34 years at diagnosis) than in their siblings and elevated HRs for mood disorders were found in females (both age groups). In addition, higher frequencies of antidepressant purchases were also detected in females in both age groups.

Conclusions: Childhood BT and leukemia/NHL survivors seem to require special educational support after their cancer treatments, and since childhood cancer survivors are at risk for premature retirement, adequate social support should be provided. There is a need for aftercare psychological support, especially for female childhood and AYA cancer survivors.

Keywords: cancer, children, young adults, psychosocial, late-effect

TIIVISTELMÄ

Ritva Ahomäki

Psykososiaalinen selviytyminen nuorena sairastetun syövän jälkeen

Turun yliopisto, Lääketieteellinen tiedekunta, Lastentautioppi, Turun kliininen tohtoriohjelma, Turun yliopistollinen keskussairaala, Lasten ja Nuorten klinikka.

Annales Universitatis Turkuensis, Medica-Odontologica, Turku, Suomi, 2018

Tausta: Lapsena ja nuorena aikuisena syövän sairastaneiden määrän kasvaessa myös syövän aiheuttamien myöhäisvaikutusten ilmaantuvuus on lisääntynyt. Syövän sairastaneet tarvitsevat strukturoitua seurantaa, ja tehokkaiden tukimuotojen löytämiseksi tarvitaan lisää tutkimustietoa.

Tutkimuksen tarkoitus ja metodit: Lapsena ja nuorena aikuisena syövän sairastaneiden psykososiaalisen selviytymisen tutkimiseksi, teimme neljä retrospektiivistä, kansallisiin rekisteritietoihin perustuvaa analyysiä. Ensimmäisessä osatyössä tutkittiin lapsena syövän sairastaneiden peruskoulun jälkeistä koulutusta ja sosiaalista selviytymistä. Seuraavassa osatyössä selvitettiin, ovatko muuttuneet terveystarkastusohjeet lisänneet lapsena syövän sairastaneiden sisäänottomääriä varuspalvelukseen, ja miten syövän sairastaneet suoriutuvat armeijan fyysisissä sekä kognitiivisissa testeissä. Kahdessa viimeisessä osatyössä tutkittiin lapsena ja nuorena aikuisena syövän sairastaneiden psykiatrista sairastuvuutta (HILMO-rekisterin psykiatriset diagnoositiedot) sekä masennuslääkeostotietoja (Lääkeostorekisteri) sisarusverrokkeihin nähden.

Tulokset: Lapsena syövän sairastaneista suurempi osa jäi ilman peruskoulun jälkeistä koulutusta väestöverrokkeihin nähden. Sen sijaan lapsena syövän sairastaneilla ei havaittu suurentunutta riskiä työttömyyteen, mutta riski varhaiseen eläköitymiseen oli selvästi suurentunut kaikissa syöpäryhmissä. Lapsena sairastettu syöpä oli yhä merkittävä armeijaan pääsyn hylkäyssyy, mutta palvelukseen otetut syövän sairastaneet suoriutuivat pääosin hyvin armeijapalveluksessa. Riski aivojen orgaaniseen-/muistisairauteen havaittiin olevan suurentunut molemmissa tutkituissa ikäryhmissä (0-19 ja 20- 34-vuotiaana syöpädiagnoosin saaneet) ja naisilla havaittiin kaikissa ikäryhmissä enemmän mielialamuutoksia sekä masennuslääkeostoja kuin verrokeilla.

Johtopäätökset: Lapsena aivokasvaimen tai leukemian/NHL:n sairastaneet saattavat tarvita tuen tarpeen kartoitusta kouluiässä, ja lapsena syövän sairastaneiden riittävän sosiaalinen tuen järjestäminen on tärkeää, jotta varhainen eläköityminen voidaan ehkäistä. Etenkin tytöt ja naiset tarvitsevat psykologista tukea sairastetun syövän jälkeen.

Avainsanat: syöpä, lapset, nuoret aikuiset, psykososiaalinen, myöhäisvaikutus

TABLE OF CONTENTS

ABBREVIATIONS

AD	Antidepressant medication
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
ATC	Anatomical therapeutic chemical
AYA	Adolescents and young adults
BT	Brain tumor
CAYAS	Childhood, adolescent, young adult survivors
CCLG	Children's Cancer and Leukemia Group
CCSS	Childhood Cancer Survivor Study
CI	Confidence interval
CNS	Central nervous system
COG	Children's Oncology Group
CRT	Cranial irradiation therapy
DIPG	Diffuse intrinsic brainstem gliomas
DPR	Drug Purchase Register
FAMOS	Family oriented support
FCR	Finnish Cancer Registry
FDF	Finnish Defence Forces
fMRI	Functional Magnetic Resonance Imaging
GPOH	German Society for Pediatric Oncology and Hematology
HADS	Hospital Anxiety and Depression Scale
HD-MTX	High-dose methotrexate
HDR	Hospital discharge register
HL	Hodgkin lymphoma
HR	Hazard ratio

ICD-10	International classification of diseases and related health problems, tenth revision
LTFU	Long-term follow-up
MTX	Methotrexate
N	Number
NA	Not applicable
NCCS	National Coalition for Cancer Survivorship
NHL	Non-Hodgkin lymphoma
PIC	Personal identification code
PRC	Population Register Centre
PTSD	Post-traumatic stress disorder
SALUB	Swedish Working Group for Long-Term Follow-up after Childhood Cancer in Sweden
SF	Statistics Finland
SII	Social Insurance Institution Register
SJLIFE	St. Jude Lifetime Cohort Study
Sympathetic	Neuroblastoma and other sympathetic system tumors
YA	Young adult

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by Roman numerals (I-IV).

I Ahomäki R, Harila-Saari A, Matomäki J, Lähteenmäki PM. Non-graduation after comprehensive school, and early retirement but not unemployment are prominent in childhood cancer survivors - a Finnish registry-based study. J Cancer Surviv. 2017;11(2):284-294.

II Ahomäki R, Harila-Saari A, Parkkola K, Matomäki J, Lähteenmäki PM. Compulsory Military Service as a Measure of Later Health in Male Survivors of Childhood Cancer. Acta Oncol. 2017; 56(12):1712-1719.

III Ahomäki R, Gunn ME, Madanat-Harjuoja LM, Matomäki J, Malila N, Lähteenmäki PM. Late psychiatric morbidity in survivors of cancer at a young age: a nationwide registry-based study. Int J Cancer 2015;137(1):183-92.

IV Ahomäki R, Kero AE, Madanat-Harjuoja LM, Koivisto M, Malila N, Lähteenmäki PM. Purchases of antidepressants after cancer at a young age in Finland. Manuscript.

1 INTRODUCTION

The advances in cancer treatments and supportive care during recent decades have resulted in a continual increase in the 5-year survival rates of cancer patients throughout Europe (Gatta et al. 2014), (Hovaldt et al. 2015), (Asdahl et al. 2015). Overall 5-year survival rate of childhood cancers is 77.9% (Gatta et al. 2014). In adult cancers, 5-year survival rates vary from 18% to 39% in adult ALL patients (De Angelis et al. 2014), (Allemani, Coleman & CONCORD Working Group 2015) to 85% in breast cancer (Allemani, Coleman & CONCORD Working Group 2015). In EUROCARE 5 data, about a third of all adult cancer cases had 5 year survival greater than 80%, whereas about a quarter had survival below 30% (De Angelis et al. 2014).

It has been estimated that approximately 75 % of childhood cancer survivors are confronted by adverse late effects associated with their cancer treatment (Geenen et al. 2007), and 40 % of survivors experience severe health disabilities and around 30% of pediatric cancer survivors suffer from several adverse effects (Oeffinger et al. 2006). Childhood cancer survivors may encounter new morbidities, such as endocrine (Tonorezos et al. 2015), (Taylor et al. 2009), cardiovascular (Mulrooney et al. 2016), (Kero et al. 2013) as well as psychological symptoms (Lund et al. 2013), (Ander et al. 2016), and educational problems (Lund et al. 2013),(Jacola et al. 2016) , or even premature mortality (Oeffinger et al. 2006), (Reulen et al. 2010), (Mertens et al. 2008). In assessments of cumulative incidence (Asdahl et al. 2015) and burden of disabilities and comorbidities after cancer (Bhakta et al. 2017) survivors of childhood cancer have been reported to have at least a doubled disease burden compared to healthy controls. However, there has been only a limited description of the late-effects occurring after cancer has been diagnosed in adolescence or young adulthood (AYA). The first comprehensive review of the published literature specifically focusing on the late-effect spectrum was published in 2011 without any clear age specific conclusions (Woodward et al. 2011).

The assessment of treatment related late effects can be carried out with large cancer survivor cohorts by examining associations between given doses of chemotherapy-, and irradiation (Asdahl et al. 2015) and the reported adverse effects. Treatment associated late effects may persist after the treatment has ended, and there may well be effects occurring several years after cancer diagnosis (Salz et al. 2015). It is to be noted that certain deficits e.g. on neurocognition may subsequently affect the cancer survivors (Hawkins, Robison 2006), (Boman et al. 2009), (Reimers, Mortensen & Schmiegelow 2007), (Armstrong et al. 2013), (Reddick et al. 2014). It has been claimed that those survivors facing severe functional/psychosocial adverse outcomes would benefit from supportive interventions (Willard et al.

2017). The approach in these interventions should be individualized, so that the allocation of resources of follow-up care and means of support for cancer survivors would be organized in a co-ordinated manner (Davies, Batehup 2011).

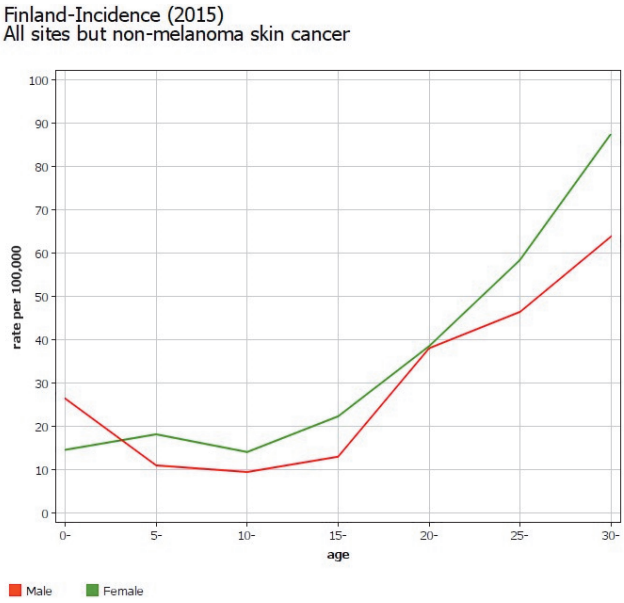
The Finnish national health care and statistics registries have enabled researchers to conduct studies on childhood and AYA cancer patients as they age and reach later life. The studies included in this thesis contain data on educational and psychosocial outcomes of childhood and AYA cancer patients. Novel data especially on young adult (YA) cancer survivors' psychiatric outcomes, were obtained. It is predicted that the reported results might assist in the planning of more individualized after-care for childhood and AYA cancer survivors

2 REVIEW OF LITERATURE

2.1 Cancer at a young age

2.1.1 Incidence and survival

From the national cancer registries, data on cancer incidences can be retrieved in 5 year categories (Figure 1). The numbers of annual new cases can be classified, e.g., from 0-19 years referring to childhood and adolescent cases, and from 20-34 years referring to young adult statistics (Figure 2).



Age-group	Male	Female	Average
0-4	26.31	14.46	20.4
5-9	10.87	18.05	14.5
10-14	9.34	13.96	11.7
15-19	12.88	22.21	17.6
20-24	37.92	38.41	38.2
25-29	46.34	58.34	52.4
30-34	63.75	87.46	75.1

Figure 1. Incidence of cancer cases by age-categories.

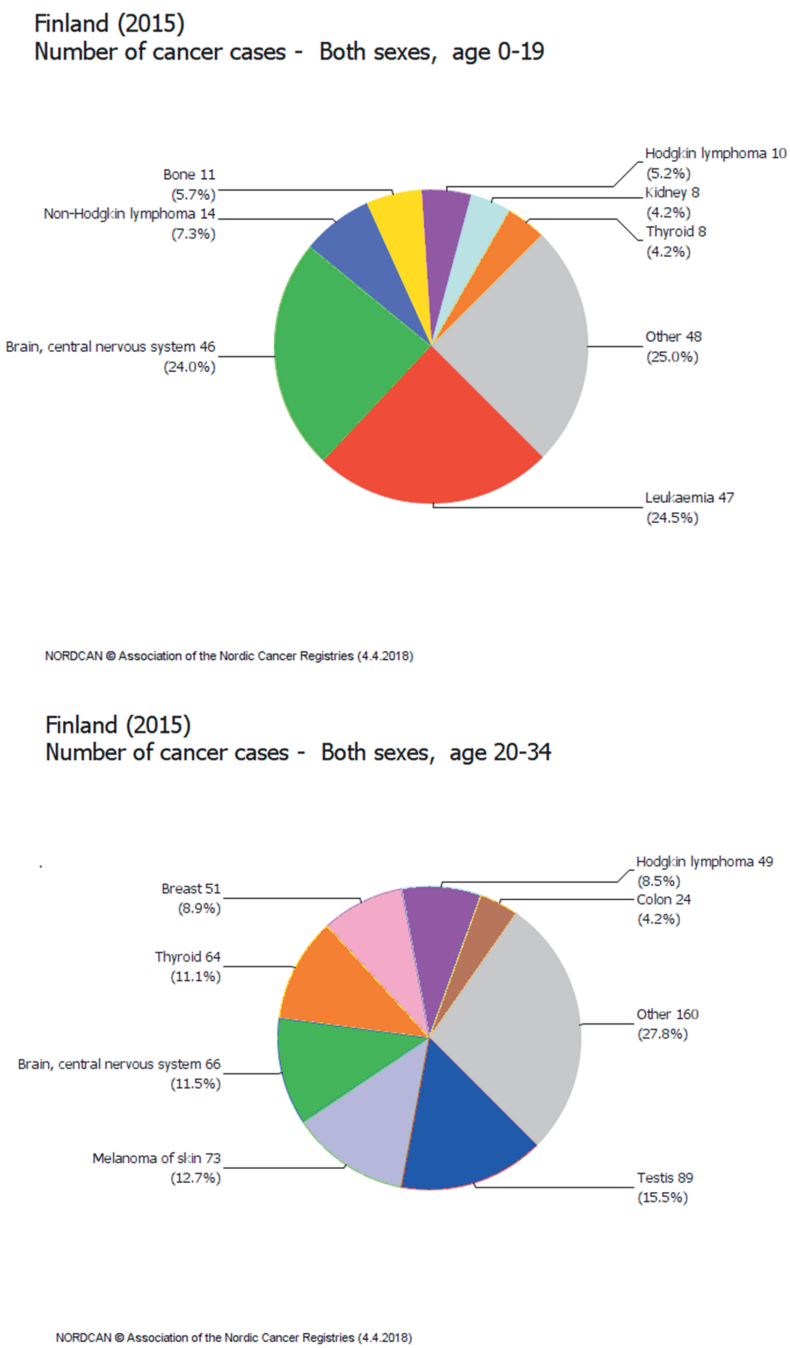


Figure 2. The cancer cases in both sexes (year 2015), subdivided by age groups (younger age group 0-19 years at cancer diagnosis (n= 192) and older group 20-34 years at cancer diagnosis (n=576). Data retrieved with the NORDCAN tool.

Mostly childhood and adolescent malignancies consist of acute lymphoblast leukemias (ALL), CNS malignancies, and Hodgkin lymphomas (HL) followed by

substantially lower numbers of other cancers e.g. Wilm's tumors, neuroblastomas and hepatoblastomas (Figure 1b). In contrast, the largest groups of malignancies in young adults (20-34 years at diagnosis) are testis tumors, melanomas and CNS tumors followed by thyroid cancer and lymphomas (Figure 2, lower panel).

According to several studies, overall 5-year survival rates after early age onset cancer have been progressing to the level of 80% during last five decades; this is attributable to some major improvements in cancer treatment. However, the greatest advances in improving survival rates occurred before the year 2000 (Armstrong et al. 2009b), (Geenen et al. 2007), (Armstrong et al. 2011), (Gatta et al. 2014), (Toft et al. 2017). In a Finnish population based register study, the overall survival of childhood cancer (diagnosed below 15 years of age) was 82.1%. The survival rates of the main cancer groups were as follows: 86.3 % (ALL), 97.2 % (HL) and 79.1 % (CNS malignancies) (Madanat-Harjuoja et al. 2014).

In 2014, Gatta et al reported that the European 5- year overall survival of childhood cancer (diagnosed before 15 years of age) was 77.9%; in pediatric ALL it was 86.3%, in HL, it was even better, 95.4% but for CNS malignancies, the survival was 57.5% (Gatta et al. 2014). Thus, the Finnish figures are admirable, even when compared with North European values: overall 81.2%, ALL 86.7%, HL 95%, CNS malignancies 65.4% (Gatta et al. 2014). However, some very rare childhood cancer diagnoses, such as diffuse intrinsic brainstem gliomas (DIPG), highly malignant gliomas and metastatic sarcomas, persist in having limited survival rates (Smith et al. 2014).

With regard to the survival of young adult patients with malignancies, the international reports are more difficult to assess. In a survey of European cancer patients diagnosed up to 2007 at the age from 15 years and above, the tumors with the good survival at 5 years were testicular cancer (88.6%), thyroid cancer (86.5%), skin melanoma (83.2%), breast cancer (women only;81.8%) and HL (83.2%) (De Angelis et al. 2014).

Because of increased survival rates and possible treatment induced late-effects (Armstrong et al. 2009b), (Geenen et al. 2007), the psychosocial impact of cancer and its treatment on survivors' lives have become an important issue (Kahalley et al. 2013). The body of literature on late-effects for childhood and adolescent cancer patients has grown exponentially, but nonetheless, little is known about the quality of survival in patients diagnosed with cancer in young adulthood.

The research into pediatric and YA cancer survivorship has been based on large cohorts gathered from several countries. Cohort studies, like the Childhood Cancer Survivor Study (CCSS), have attempted to assess late effects both in a longitudinal setting and by making retrospective observations. Furthermore, they have evaluated risks for various late sequelae (Leisenring et al. 2009). Thus, a broad

range of methodologies have been applied in investigations into cancer survival and late-effects; these have included epidemiological and clinical approaches such as record linkage studies, questionnaire studies, interview based surveys and physical and psychological examinations (Hawkins, Robison 2006). The largest cohort studies are presented in Table 1.

Table 1. The description of the largest, global young age onset cancer research cohorts. The table includes data on the eras and ages at cancer diagnosis, cohort sizes, reference groups, study designs and outcome assessments.

STUDY	ERA AND AGE AT CANCER DIAGNOSIS	COHORT SIZE	REFERENCE GROUP	STUDY DESIGN	OUTCOME ASSESSMENT
CCSS (Robison et al 2009) Childhood Cancer Survivor Study	1970-1986 <21 years	20 720	Siblings	Multicenter retrospective cohort	Questionnaires, medical evaluation, patient records
GCCR (Petersen et al 2013) German Childhood Cancer Register	1980-2009 <15 years	46 115	General population	Multi-center institution-based cohort	Questionnaires, registry-based data
BCCSS (Hawkins et al 2008) British Childhood Cancer Study	1940-1991 <15 years	17 981	not mentioned	Population-based, retrospective cohort	Questionnaires
CAYACS (Zhang et al 2012) Childhood, adolescent and young adult cancer survivors	1970-1995 <25 years	3 841	Matched, general population	Population-based, retrospective cohort	Registry-linkage
SCCSS (Kuehni et al 2012) Swiss Childhood Cancer Survivors Study	1976-2003 0-20 years	5 553	General population, siblings	Population-based, retrospective cohort	Registry-linkage, medical evaluation, questionnaires
AliCCS (Holmqvist et al 2014) Adult Life after Childhood Cancer in Scandinavia	1943-2008 <19 years	33 160	General population	Population-based, retrospective cohort	Registry-linkage
SJLIFE (Hudson et al 2013) St Jude for Life Memphis, Tennessee, USA	1962-2001 <21 years	3 900	not mentioned	Single-center, retrospective and pro-spective aim	Medical evaluations, questionnaires
FCRC (Madanat-Harjuoja 2008) Finnish Cancer Registry Cohort	1953-2004 <35 years	25 784	General population, siblings	Population-based, retrospective cohort	Registry-linkage
NCCC (Garwicz et al 2012) Nordic Countries Childhood Cancer Cohort	1960-1999 <20 years	37 515	General population	Population-based, retrospective	Registry-linkage
EKZ/AMC (Sieswerda et al 2013) Emma Children's Hospital Academic Medical Center	1966-2003 <18 years	1 822	not mentioned	Single-center, retrospective and prospective aim	Questionnaires

2.1.2 The follow-up care of the survivors

As young cancer survivors age into adulthood, treatment-related adverse effects occur. The complexity of possible late-effects is presented in Figure 3.

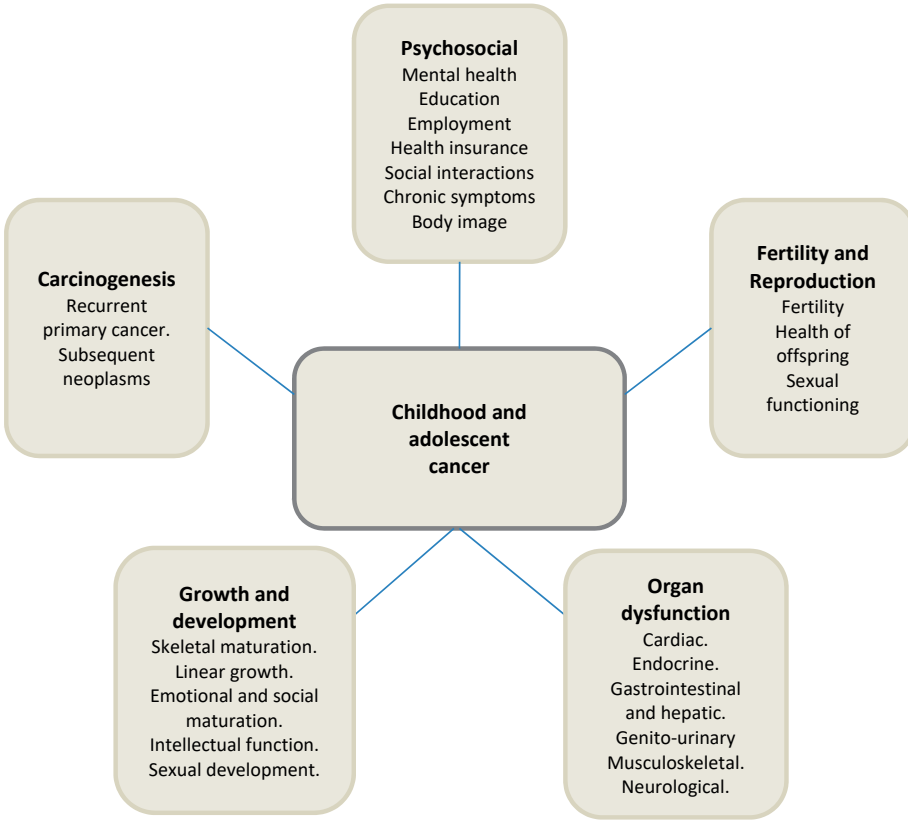


Figure 3. The spectrum of late-effects after childhood and adolescent cancers. Modified from Robison et al. 2014.

Thus, it has been recommended that there should be an implementation of evidence-based guidelines for long-term follow-up (LTFU) (Kremer et al. 2013), (Hawkins, Robison 2006). Frequently, the survivors of low- and intermediate risk cancer groups have been treated only by general practitioners later in life, and this has been associated with poorer late effect detection and less survivorship focused care (Nathan et al. 2013), (Szalda et al. 2016). Disengagement from follow-up has also been reported, especially in the transitional phase to adult care (Brier, Schwartz & Kazak 2015), (Lund et al. 2011b), (Wiener et al. 2012), (D'Agostino, Penney & Zebrack 2011), since 66 % of survivors of childhood and adolescent cancer have been provided with an opportunity to participate in long-term follow-up (LTFU) before they reach adult age (Essig et al. 2012) whereas the corresponding number in adult care has been much lower, 38% (Essig et al. 2012).

One of the first late effect screening guideline systems was created in North America, where the Long-Term Follow-up Guidelines for Survivors of Childhood, Adolescent and YA cancer were established by the Children's Oncology Group (COG) in 2004 (Landier et al. 2004), (Bitsko et al. 2016). Specialists have conducted comprehensive treatment related risks and estimated exposures, evidence-based health care and education of survivors also in Europe. Several national guidelines have been created e.g. in the UK by the Children's Cancer and Leukemia Group (CCLG), the Swedish Working Group for Long-Term Follow-Up after Childhood Cancer in Sweden (SALUB), and the German Society for Pediatric Oncology and Hematology (GPOH). By assessing several national LTFU guidelines, the European collaboration of pediatric oncologists merged the best clinical practices into the Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer (Pancare) in 2011 (Brown et al. 2015), (Hjorth et al. 2015). In an attempt to achieve a universal approach in the best clinical care of the cancer survivors, an international collaboration was initiated in 2010 to achieve harmonization of CPGs (clinical practice guidelines) for the follow-up care of childhood cancer survivors (Kremer et al. 2013).

Previously, there has been a paucity of knowledge of the effect of CCS's follow-up care, but recently some studies have investigated this topic. Several studies have highlighted the positive impact and possible gains of LTFU guideline usage. Most of these studies have been based on the COG guidelines (Landier et al. 2015), (Lindell et al. 2015), (Blaauwbroek et al. 2007). In a US study, it was indicated that survivors attending specialized follow-up care had twice the incidence of detected endocrine and hormone-related late effects compared with non-attendees (Ford, Chou & Sklar 2013). Furthermore, the disengaged were experiencing a lower quality of life because of physical and social deficits (Blaauwbroek et al. 2007).

The need for psychosocial care in follow-up has become apparent because of these psychosocial adverse effects. Dieluweit et al. found that only 44% of adolescent cancer survivors had received adequate care for their psychosocial needs (Dieluweit et al. 2011). In North America, the National Coalition for Cancer Survivorship (NCCS) has implemented a framework for detection of psychosocial effects in follow-up care (Jacobs, Shulman 2017) (Figure 4, page 22).

In Sweden, HADS (Hospital Anxiety and Depression Scale) was used to screen cancer survivors' psychosocial adverse effects. In a six months follow-up, many survivors with psychosocial support reported still-ongoing problems. However, the levels of anxiety decreased and the quality of life seemed to improve with time (Thalen-Lindstrom et al. 2013), (Ander et al. 2016).

Different algorithms have also been developed to evaluate the need for psychosocial support, such as a family-oriented strategy devised in Denmark (FAMOS=family-oriented support) (Salem et al. 2017) and a few other web-based interventions (Kessler et al. 2016), (Kanera et al. 2016). FAMOS was found to help families with childhood cancer survivors to cope better with this home-based intervention aimed at post-cancer symptoms such as PTSD (post-traumatic stress disorder), mood disorders, and anxiety than could be achieved with conventional care. The initial results seemed promising, while a more detailed study on the effects of this intervention is being conducted (Salem et al. 2017). A German study of an internet-based psychotherapy program implemented for AYA cancer survivors, showed that survivors obtained helpful tools for dealing with PTSD and anxiety symptoms (Seitz et al. 2014a), (Seitz et al. 2014b). In adult care, various web-based self-reports of distress and interventions for reducing these symptoms after cancer treatments, have been implemented (Berry et al. 2014), (Ruland et al. 2013), (Hoybye et al. 2010). Some of these electronic interventions include educational and medical care related contents (Kuijpers et al. 2015) or telecare (Kroenke et al. 2010) in addition to self-reports. Improvements in psychosocial functioning of adult cancer survivors have been detected in a recent Dutch study, though better outcomes were associated with higher a educational level of survivors in this web-based intervention (Willems et al. 2017).

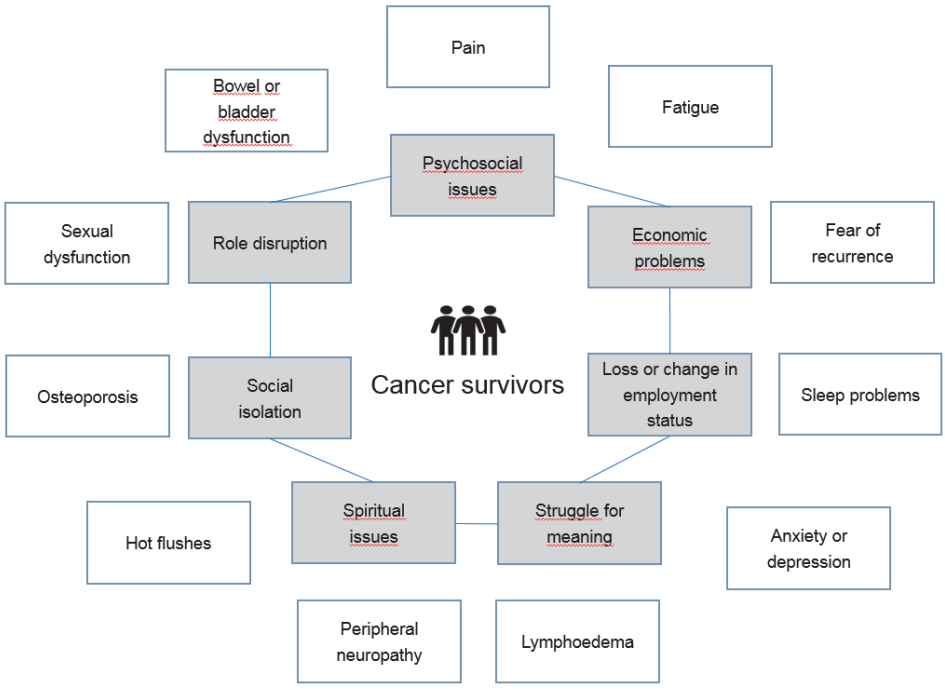


Figure 4. Interrelations of possible long-term late effects of young onset cancer survivors. Modified from Jacobs LA et al 2017.

2.2 Late effects after young age onset cancer

2.2.1 An overview of late effects

While remarkable advances in childhood cancer treatment have been achieved, survivors may well encounter new forms of morbidity even after long period of time (Figure 3, page 19). Therefore, longitudinal clinical trials and register-based studies are needed to collate valuable information on childhood cancers survivors and their long-term outcomes (Armstrong et al. 2016), (Kremer et al. 2013), (Hjorth et al. 2015). Survivors and their healthy peers naturally share certain risk factors of late morbidity, such as lifestyle, environmental exposure and genetic factors, and these need to be taken into consideration in the follow-up evaluation (Hovaldt et al. 2015).

In the Nordic countries, it has been estimated that childhood cancer survivors experience an overall mortality rate which is 10 times higher than in general population (Moller et al. 2001) with cancer recurrence being the most common reason for this statistic, followed by secondary malignancies, and cardiac and pulmonary causes. The same findings have been reported in many international studies (Mertens et al. 2002), (Armstrong et al. 2009a), (Krull et al. 2012), (Garwicz et al. 2012), (Lund et al. 2011a), as well as in Finland (Kero et al. 2015). Five year survival after second primary cancer seems to be worse in some cases, especially in adolescents with secondary HL or BT compared to the same primary malignancies in adolescence, and partially because of this fact, survival improvements have been more modest in the AYA age group than in the other age groups (Keegan et al. 2017).

The late morbidity of childhood cancer survivors has been significantly higher than the general population and it has been associated with cancer treatment induced late effects (Oeffinger et al. 2006). Radiation has been acknowledged as evoking late-effects in several organs. Cardiovascular, neurologic, endocrine, neurocognitive, and psychosocial late effects, as well as, secondary malignancies have been reported (Armstrong et al. 2009a), (Lindell et al. 2015), (Krull et al. 2014). The Childhood Cancer Survivor Study revealed that the proportion of patients receiving radiotherapy was 77% in the 1970s, while the corresponding percentage was only 41 % in the 1990s (Armstrong et al. 2016). Innovations in radiotherapy technology, like intensity modulated radiotherapy, modified fractionation and proton therapy, have allowed better sparing of the healthy tissues around the target organs (Thariat et al 2013). The chemotherapeutic agents are being used more extensively than in previous decades, e.g., anthracycline-induced cardiotoxicity has been acknowledged (Leger et al. 2015). In fact, cumulative

chemotherapy doses seem to have diminished and therefore, less adverse effects might develop nowadays (Armstrong et al. 2016).

2.2.2 Neurocognitive complications and educational level after young age onset cancer

As patients are treated with multi-modal treatment protocols, the frequency of neurocognitive sequelae may increase simultaneously as the population of cancer survivors continues to expand. The assessment of neurocognitive adverse effects in childhood cancer survivors has mostly been based on patient interview surveys (e.g. CCSS studies). Several methods for evaluating neurocognitive capacity have used in these studies: e.g. the Wechsler Intelligence Scale, the Amsterdam Neuropsychological Test, and Delis-Kaplan Executive Function System (Keifer, Tranel 2013). In a few Scandinavian studies, research on neurocognitive sequelae has been based on the national registry data, which has enabled the long-term assessment of adverse effects of young age onset cancer. Additionally, as certain treatment regimens may cause brain tissue damage, structural neuroimaging (e.g functional magnetic resonance imaging, fMRI) can be used to evaluate neurocognitive function after childhood cancer (Monje et al. 2013), (Brinkman et al. 2012).

The reports on cognitive deficits after childhood cancer have shown that survivors experience learning difficulties more frequently than their healthy peers and that deficits may appear years after cancer treatment and may be of progressive nature (Bonneau et al. 2011), (Harila-Saari et al. 2007), (Lahteenmaki et al. 2008), (Reimers et al. 2003). In Finland register-based data from FCR and Statistics Finland have enabled investigations to be conducted into educational outcomes of childhood cancer survivors. Female gender, younger age at diagnosis (Di Pinto et al. 2012), (Lorenzi et al. 2009), (Nathan et al. 2007), (Koch et al. 2004), genetic predisposition, cancer type, age, and treatment modalities (Shortman et al. 2014), (Lancashire et al. 2010), (Ross et al. 2004), especially cranial irradiation (Turner et al. 2009), have been recognized as factors associated with neurocognitive complications. The need for special education at school is one of the manifestations of neurocognitive late-effects (Mitby et al. 2003). Furthermore, patients diagnosed with cancer during adolescence are thought to have an elevated risk for developing dysfunctions in their cognitive capacity and, therefore, education after high school graduation or the progression to further education may be delayed (Dieluweit et al. 2011), (Armstrong et al. 2015).

There have been relatively few reports on childhood cancer survivors' non-compulsory education; the findings indicate that cancer survivors, particularly

brain tumor survivors, are more likely to have only compulsory training, but nonetheless a few childhood cancer survivors achieve a university degree (Kuehni et al. 2012). Furthermore, females and BT survivors are reported to have a higher risk for not attaining any degree than males and other solid tumor survivors (Lancashire et al. 2010).

Several studies have been conducted on the neurocognitive sequelae caused by cranial irradiation therapy (CRT), but especially in high-risk cases, multi-modal treatment protocols are essential and, thus, CRT cannot be avoided. CRT has consistently been shown to impair visuomotor accuracy, attention ability and visuospatial outlining (Reddick et al. 2014), (Campbell et al. 2007), (Kadan-Lottick et al. 2010). The neurocognitive outcomes of chemotherapy-only treatment seem to be milder than after CRT (Harila et al. 2009), (Krull et al. 2013a), (von der Weid et al. 2003), but there are some indications of deficits in attention, processing speed and decreasing hippocampal function after the end of chemotherapy (Conklin et al. 2012), (Essig et al. 2014). Furthermore, learning and memory functions might be damaged due to chemotherapy or radiation therapy, most probably caused by white matter damage (Askins, Moore 2008).

In earlier treatment times, since there were some similarities in childhood cancer treatment procedures, children with brain tumor, ALL, or non-Hodgkin lymphoma (NHL) appeared to have the highest risk for experiencing neurocognitive sequelae (Reimers et al. 2003), (Campbell et al. 2007), (Essig et al. 2014), (Boman, Lindblad & Hjern 2010), (Lahteenmaki et al. 2007), (Hardy et al. 2013). However, self-reports on cognitive deficits and psychological distress have detected an increased risk for functional limitations also in survivors of adolescent and young adult cancers (Prasad et al. 2015).

2.2.3 Cardiovascular, pulmonary and metabolic late effects

Multiple cardiovascular late effects have been reported after childhood and AYA (adolescent and young adult) cancer in several cohort studies (Mertens et al. 2008), (Lipshultz et al. 2012), (Prasad et al. 2012). These are largely due to the cardiotoxic effects induced by either anthracycline drugs or thoracic directed radiation therapy (Mulrooney et al. 2016). Cardiovascular effects are associated with a higher risk for mortality and physical inactivity (Kero et al. 2013), (Miller et al. 2013), (Mulrooney et al. 2009).

The major risk factors for adverse cardiovascular outcomes are as follows; obesity, smoking, physical inactivity, hypertension, and dyslipidemia (Mulrooney et al. 2016). Many of these factors seem to become more prevalent as cancer survivors

are aging (Armstrong et al. 2009). As a way to prevent cardiovascular morbidity and mortality, web-based interventions could be used to convince cancer survivors to exercise more or encourage them to remain non-smoking (Kanera et al. 2017). Cancer survivors have been suggested to have a sevenfold risk to die due to cardiovascular deficits (Mertens et al. 2008). Cardiovascular morbidity refers to cardiomyopathy, coronary artery disease (CAD), valvular deformities and dysfunction, arrhythmias and hypertension (Tai et al. 2012). Especially younger patients who have received large mediastinal radiation doses (over 15 Gy), and males exposed to higher doses (≥250 mg/m2) of anthracyclines, experience an increased risk for cardiomyopathy and valvular deformities (Machann et al. 2011), (Mulrooney et al. 2016).

In addition to the clinical manifestations of cardiovascular outcomes, the occurrence of asymptomatic cardiovascular findings has been reported after radiation and also after contemporary treatment protocols. These symptoms may also have contributed to poor physical performance in these individuals (Leger et al. 2015).

Since lung tissue is sensitive to chest radiation-, chemotherapy- or surgery induced deficits, a significant number of childhood and AYA cancer survivors may increasingly experience pulmonary late effects as they age (Armenian et al. 2015). The occurrence of pulmonary deficits, like asthma, emphysema, lung fibrosis, and chest wall deformities has been found to be more likely in survivors of young age onset cancer in comparison with their siblings (Huang et al. 2014), (Prasad et al. 2012). Poorer physical functioning and the occurrence of respiratory symptoms have been associated with diffusion capacity problems in female survivors (Armenian et al. 2015). In a report from the SJLIFE (St. Jude Lifetime Cohort Study), measurements of lung function markers and results of six-minutes walking test were analyzed and poorer exercise performance was found in adult survivors of childhood cancer (Green et al. 2016).

2.2.4 Socio-economical outcomes

A follow-up on social outcomes of childhood and AYA cancer survivors has also been performed (Mertens et al. 2008). Several studies have reported childhood and AYA cancer survivors to have an excessive risk for unemployment or part-time work, when compared either their siblings or healthy controls (Pang et al. 2008), (Ellenberg et al. 2009). Survivors of brain tumors have been suggested to have as much as five times higher risk for unemployment than controls, although ALL survivors only display a trend towards this outcome (de Boer, Verbeek & van Dijk 2006). Furthermore, existing studies have revealed an association between

cognitive impairment, unemployment and lower educational level (Ehrhardt et al. 2017). In contrast, some American studies have found unemployment as being of little importance in the spectrum of late-effects (Crom et al. 2007), (de Boer, Verbeek & van Dijk 2006), (Kirchhoff et al. 2011), (Armstrong et al. 2015), (Hudson et al. 2013) and similar findings have been reported in a few European studies (de Boer, Verbeek & van Dijk 2006), (Ottaviani et al. 2013).

Somatic deficits may be the origin for negative social outcomes of survivors, because of decreased physical functioning (Tai et al. 2012). Furthermore, these deficits may lead to lower income levels in survivors, as has been reported (Armstrong et al. 2015), (Kirchhoff et al. 2011). On the other hand, the higher the parental educational and income level, the better seems to be the social outcomes of survivors (Wolfe et al. 2013), (Dalton et al. 2008). In a Norwegian study, cancer survivors' social outcomes were examined in association with mortality. Being a single child, and the mother's higher educational level were both associated with reduced mortality in survivors (Syse, Lyngstad & Kravdal 2012) Similarly, in a Danish register-based study, better cancer survival was found in solid tumor survivors whose parents had higher education and in those who were an only child. Furthermore, CNS tumor survivors were postulated to have better outcomes in families where the parents were living together (Simony et al. 2016).

The very experience of cancer and the resulting cancer treatment disrupt normal social life and affect the cancer survivor's social relations, and possibilities for independent living (Schultz et al. 2007). Female cancer survivors, particularly childhood BT survivors, have been reported to be married less frequently than their age-matched controls (62% vs 78 %) (Nagarajan et al. 2004), (Gurney et al. 2009). Existing reports show that especially survivors of childhood CNS malignancy an have elevated risk for becoming married and for living on their own (Koch et al. 2011), (King et al. 2017), (Font-Gonzalez et al. 2016). The report on the SJLIFE cohort revealed that BT survivors with auditory deficits had an increased risk for undesirable social outcomes when compared with their siblings (Brinkman et al. 2016).

2.3 Neurotoxicity of cancer treatment

2.3.1 Radiation-induced neurocognitive deficits

Radiation therapy has been an essential component of childhood cancer treatment, but especially in the treatment of ALL, the use of cranial irradiation as prophylactic treatment has been terminated to a large extent (Pui 2009). The cumulative dose,

the radiation source, fractionation, and the patient's sex and age are the factors associated with radiation-induced late effects (Armstrong, Stovall & Robison 2010). Radiation has been speculated to induce adverse effects in the brain including necrotizing leukoencephalopathy, calcifications inducing microangiopathy, cerebellar sclerosis, and spinal cord dysfunction and it has been claimed that the neurocognitive adverse effects after cranial irradiation do not achieve a plateau later in life (Packer et al. 1987). In the CCSS cohort, childhood ALL survivors (64.5% irradiated) seemed to have a higher risk for auditory-vestibular-visual (RR 1.8, 95% CI 1.5-2.2) and coordination difficulties (RR 4.1, 95% CI 3.1-5.3) compared with their siblings (Goldsby et al. 2010). BT survivors have a significantly elevated risk for neurocognitive impairment, depending on the tumor type and location as well as being due to treatment. A cranial radiation exposure exceeding 50 Gy to the posterior fossa has been associated with a higher risk of auditory deficits, whereas similar radiation doses to the frontal areas of the brain have been associated with motor function problems (Packer et al. 2003), (Figure 5 , page 29). The young age onset ALL, HL and BT survivors have been claimed to carry a marked risk for radiation-induced cerebrovascular adverse effect, including strokes (Morris et al. 2009).

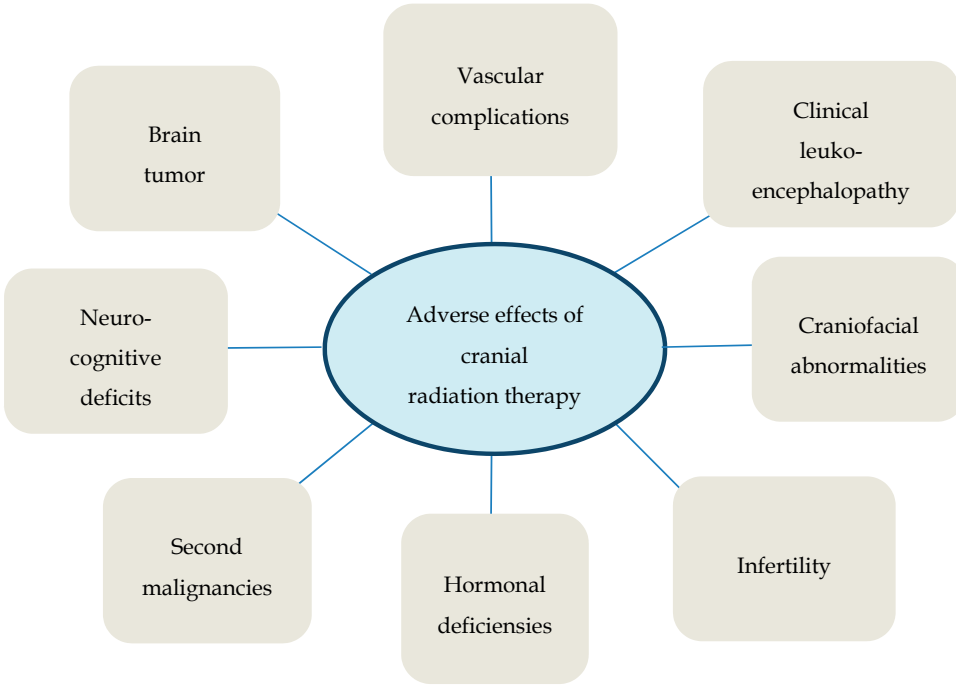


Figure 5. The adverse effects of radiation therapy.

2.3.2 Effects of chemotherapy on neurocognition

The clinical manifestations of chemotherapy-induced toxicities depend on the cumulative dose of treatment, the route of administration and the patient's age and gender at the time of diagnosis. However, the risk for neurocognitive adverse effects varies from individual by individual, and there may also be a genetic susceptibility (Bhatia 2011). Despite its toxic effects, chemotherapy has been suggested to have milder outcome effects than radiation on the survivors' life (von der Weid et al. 2003), (Harila et al. 2009), (Krull et al. 2013).

One widely used chemotherapeutic agent, methotrexate, has been associated with cerebral calcifications, a higher risk for leukoencephalopathy, and acute neurotoxicity (Mahoney et al. 1998), whereas cisplatin, as well as the other platinum agents, has been associated with sensory neural hearing loss; these effects might become apparent acutely after the beginning of the treatment (Landier et al. 2014), (de Fine Licht et al. 2017). Furthermore, chemotherapy has been associated with an increased risk for a decline in the IQ (Armstrong et al. 2011). Contemporary treatment-related effects have been widely discussed in several studies and there are reports about deficits in working memory, visuospatial capacity, visuomotor accuracy, processing speed and fine motor function (Conklin et al. 2012), (ElAlfy et al. 2014), (Daams et al. 2012). On the contrary, in a few studies chemotherapy-only protocols did not seem to be linked with any significant neurocognitive late effects when the survivors were compared with their peers (Schuitema et al. 2013), (Spiegler et al. 2006).

As cortisol plays an essential role in regulating cognitive, emotional and behavioral bodily functions (Firoozi, Besharat & Rahimian Boogar 2013), an external factor, such as high-dose methotrexate (HD-MTX) treatment, may suppress the hypothalamic-pituitary-adrenal axis and disrupt the normal regulation of corticosteroid secretion in cancer patients (Drozdowicz, Bostwick 2014). Glucocorticosteroids are one component of the treatment of lymphoblastic leukemia and different types of lymphomas, because of their antineoplastic effects (Inaba et al 2010). They may, however, induce both rapidly resolving (e.g sleep problems, hyperglycemia) and persistent side effects, such as osteoporosis, cataract or truncal obesity (Koehler 1995).

Chemotherapy induced adverse effects on neurocognition may become detectable even several years after the treatment. Alarmingly, in the SJLIFE long-term follow-up, it was stated that the discovery of new neurocognitive and neurosensory adverse effects were indicative of a premature aging process and this may impair the survivors' functional status earlier than in their age-matched counterparts (Hudson et al. 2013).

2.3.3 The development of the human brain in adolescence

The human brain undergoes a complex course of events induced by hormonal and neural changes, resulting in the maturation processes of subcortical and prefrontal brain areas (Sisk, Foster 2004). If gonadal hormone action is impaired e.g., by irradiation or chemotherapeutic agents or other disruptive activities in adolescence, the maturation process may be interrupted and social behavioral deficits may occur in adulthood. The maturation process is known to continue throughout childhood and adolescence (Primus, Kellogg 1990). It is essential that the adolescent brain possesses a high level of plasticity e.g., in order to allow for cortical maturation, and thus, the adolescent brain is still a vulnerable organ (Konrad, Firk & Uhlhaas 2013). The cognitive functions are executed in the prefrontal cortex, whereas in amygdala, neural stimuli regulate emotions and social behavior. Disturbances in these maturation processes may lead to a disruption of neural networks in adolescence and, therefore, dysfunctions in cognition may appear also in adolescent cancer survivors (Casey, Getz & Galvan 2008), (Spear 2013), (Konrad, Firk & Uhlhaas 2013).

2.4 The physical fitness of cancer survivors

2.4.1 Physical performance deficits after young age onset cancer

A previous study, indicated that BT-, bone tumor and HL survivors are physically somewhat vulnerable (Hudson et al. 2013). The physical performance after young age onset cancer may be reduced e.g., because of cardiomyopathy, endothelial damage or pulmonary late-effects of cancer treatment (Miller et al. 2013), (Hoffman et al. 2013). Treatment with thoracic radiation and anthracyclines (especially in males) has been associated with poorer maximal aerobic capacity (Tonorezos et al. 2013) whereas Devine et al. found female gender, received cranial irradiation and lower parental educational level to be risk factors for a more sedentary lifestyle (Devine et al. 2017). The cumulative dose-effect of CRT has also been acknowledged as a factor for lower physical capacity (van Dijk et al. 2013). However, physical performance may also be declined in patients treated with contemporary protocols which involve less irradiation (Ness et al. 2015). The HL survivors have been suggested to have a sevenfold risk for cardiovascular morbidity according to a CCSS cohort study (Mertens et al. 2008), and particularly survivors of childhood lymphomas, brain tumors, leukemia, and testicular malignancies have been reported as having an elevated risk for cardiovascular morbidity (Kero et al. 2013). Many cancer survivors are more likely to have a

sedentary lifestyle, which might result in challenges in weight control and therefore, especially BT survivors, are more often overweight (Ness et al. 2010).

A limb surgery or amputation due to osteosarcoma or some other bone tumor may be a cause for reduced physical fitness and musculoskeletal deformities (Fernandez-Pineda et al. 2017). Lower-extremity sarcoma survivors are more likely to be physically inactive and therefore, they may have reduced physical fitness as compared with their peers (Wampler et al. 2012). Muscular strength, as assessed by grip strength, knee extension and ankle dorsiflexion have been reported to be reduced after BT and bone tumors (Hartman et al. 2006), (Hoffman et al. 2013), (Ness et al. 2009) and this results in lower physical functioning (Hoffman et al. 2013) and even to decreased bone mineral density (Odame et al. 2006). Activating cancer survivors to improve their physical capacity by various physical exercise interventions has been topic for research and positive outcomes have been achieved in pediatric BT survivors (Piscione et al. 2017) and adult breast cancer survivors (Battaglini et al. 2014). However, many of the physical exercise studies have handled cancer survivors as one group, which complicates a more cancer-specific outcome analysis (Toohey et al. 2018). Interventions are needed in the follow-up care of cancer survivors (Piscione et al. 2017) and more detailed information on their effects would assist in devising an individualized physical exercise intervention.

2.4.2 Compulsory military service and physical performance testing in Finland

Military service is compulsory in Finland for males who have turned 18 years of age. However, previously childhood and adolescent cancer survivors were generally exempted from military service (Lahteenmaki et al. 1999). After enlistment, the conscripts are divided into fitness categories, which are assessed in tests measuring physical capacity during the first weeks of their service (Figure 8, page 48). Early age onset cancer survivors with no or only minor physical late effects usually are categorized to fitness categories A or B. Their maximal aerobic capacity is measured with a twelve minute running test (Cooper test), and musculoskeletal capacity is tested by a standing long jump (maximal muscular strength), sit-ups (body's flexor muscles, dynamic endurance evaluation) and push-ups (static endurance of body muscles, dynamic muscle strength of upper extremities) and additionally with a back muscle test. An individual's overall fitness index is calculated from these results evaluating both their aerobic and muscular fitness (Cooper 1968).

2.5 Psychiatric sequelae after young age onset cancer

2.5.1 The psychological and psychiatric sequelae after young age onset cancer

Since cancer treatment protocols require long hospitalizations, children and adolescents with cancer are not able to participate in their normal social environment. The periods of isolation may harm the normal development of social skills and the autonomy of survivors (D'Agostino, Edelstein 2013), (Kahalley et al. 2013b), (Kieran et al. 2010), particularly in adolescence, when the independency process and autonomous decision making should evolve (Geenen et al. 2007), (Kahalley et al. 2013a), (Kieran et al. 2010). These events may result in elevated psychological distress in childhood cancer survivors (Kahalley et al. 2013a), (Kazak et al. 2010), (Lund et al. 2011b). On the contrary, there are studies showing that only every second childhood cancer survivor suffers from post-traumatic stress syndrome (PTSD) after cancer or that survivors report no more distress than the general population (van der Geest et al. 2013), (Sharp et al. 2017).

A Dutch study of adult (> 18 years of age) breast cancer survivors indicated that the prevalence of depression varied from 9.4% to 66.1% and the prevalence of anxiety from 17.9% to 33.3% (Maass et al. 2015a). The risk of depression seems to peak at one year from diagnosis, but the risk remains elevated compared with controls also later in life. In contrast, the symptoms of anxiety do not appear to differ from those experienced by controls (Maass et al. 2015b), (Thompson et al. 2013). In the CCSS cohort, survivors with cardiovascular, endocrine, and pulmonary adverse effects, were found to have elevated risk for depression and anxiety (Vuotto et al. 2017).

Previously, the research into the psychiatric sequelae of childhood and adolescent cancer has mainly been conducted by questionnaire-based techniques (e.g CCSS) (Stuber et al. 2010), (D'Agostino, Penney & Zebrack 2011), (Geenen et al. 2007). In Europe, several countries have national health care registries which make it possible to also elucidate longitudinal aspects of psychiatric outcomes (Ross et al. 2003), (Lund et al. 2013), (Dalton et al. 2009). Validating outcome measures has proved to be a challenge (Wiener et al. 2006) since evaluating psychiatric/psychological adverse effects requires the adoption of a multifactorial study approach and this complexity might be increased by the fact that most of the psychiatric disorders have an onset in adolescence or young adulthood (Figure 4) (Kessler, Wang 2008), (Pirkola et al. 2005).

Younger age at diagnosis, CRT, and female gender are acknowledged risk factor also for psychosocial and psychiatric adverse effects (Schultz et al. 2007), (Nathan et al. 2007), (Zebrack et al. 2004), (Reimers, Mortensen & Schmiegelow 2007), (Ander et al. 2016). In breast cancer survivors, lower physical activity, the presence of pain, and fewer number of social supporters have been associated with depressive symptoms and insomnia (Bardwell et al. 2008). According to some studies, YAs have not been found to experience excessive psychological distress after cancer (Greenfield et al. 2010), (Pirl et al. 2009), but the risk for depressive symptoms seems to exist shortly after treatment but also to a lesser extent in later life (Tai et al. 2012), (Dalton et al. 2009).

The survivors of childhood and AYA leukemia have been found to display an increased risk for PTSD compared with controls (Stuber et al. 2010), (Kwak et al. 2013). ALL survivors' self-reports about depressive symptoms have indicated that the patients themselves experience no increased level of depression (Gordijn et al. 2013), (Kurtz, Abrams 2011), (Harila et al. 2011), although anxiety has been found to occur to a significant extent immediately after the ALL diagnosis and indications have been found for depressive symptoms in the first year after diagnosis (Myers et al. 2014). In contrast, in registry-based studies and in a Nordic interview-based study, manifestations of depression were detected in ALL survivors (Lund et al. 2013), (Hovaldt et al. 2015), (Ander et al. 2015). Corticosteroids are an essential component in ALL treatment protocols; these drugs are acknowledged to exert effects on behavior and might cause mood disorders during treatment (Hochhauser et al. 2005). Fatigue and sleeping problems have been associated with a higher prevalence of depressive disorders (Daniel et al. 2015). In a recent Norwegian registry-based study, it was found that in particular young age onset (diagnosis at the age 0-25 years) CNS tumors, testicular tumor and bone- and soft tissue sarcoma survivors carried a higher risk for suicide than healthy controls (Gunnes et al. 2017).

Due to the more intensive treatment procedures and tumor location, BT survivors have been reported to experience an increased risk for suffering a higher rate of adverse late effects, along with psychiatric outcomes (Oeffinger et al. 2006), (Zeltzer et al. 2009), (Shah et al. 2015), (Turner et al. 2009). In the literature, depression and anxiety have been reported to be the most common psychiatric morbidities encountered in BT survivors (Brinkman et al. 2016), (Schultz et al. 2007), (Turkel, Tishler & Tavare 2007), (Zeltzer et al. 2009). In addition, the prevalence of psychosis and CRT induced schizophrenia might be increased in BT survivors. There are also reports that BT survivors have a higher risk for requiring psychiatric hospitalizations than the general population (Ross et al. 2003), (Turkel, Tishler & Tavare 2007).

In a Swiss study of childhood cancer survivors, a higher risk for elevated alcohol consumption was noted than in the general population (Rebholz et al. 2012). However, in a US study, substance use was less common in childhood cancer survivors than in controls, although increased marijuana use was associated with male gender, depression and higher social status (Milam et al. 2016). Behavioral disorders such as aggression, antisocial patterns and irritability have also been described but to a lesser extent than other disorders (Schultz et al. 2007), (Daszkiewicz et al. 2009).

There are fewer studies focusing on psychiatric outcomes of adulthood solid tumor survivors, but thyroid- and hormone-related cancer survivors (e.g. breast -and prostate cancers) are reported to have a higher risk for distress and depression than controls (Gorman et al. 2010), (Roerink et al. 2013), (Khan et al. 2010a), (Lund et al. 2013).

2.5.2 Antidepressant medication and cancer patients

Certain psychiatric disorders, like depression, may exert a negative impact on cancer survivors' quality of life and functional performance. Furthermore, they may also increase the survivors' usage of health care services contributing to excessive health care costs (Fujisawa et al. 2016), (Pan, Sambamoorthi 2015). In the Nordic countries, register-based data have been available for decades. Previously, the Finnish studies have examined psychiatric disorders and their treatment in the general population (Pirkola et al. 2005), (Kasteenpohja et al. 2015). Their findings have revealed a significant risk for depression in females and disease related associations of psychiatric disorders (Pirkola et al. 2005).

The antidepressant medication (AD) prescription practices in the general population have been found to differ from country to country, even inside Europe. AD prescriptions of childhood cancer survivors have been claimed to depend on the cancer type and the time elapsing from diagnosis, but also practices concerning how antidepressants are prescribed to cancer survivors may vary to a large extent between countries (Pearson et al. 2015), (Gyllenberg et al. 2011), (Johannsdottir et al. 2017). A general practitioner may prescribe AD medication to adult survivors in Finland, while childhood and adolescent patients are treated exclusively by doctor's specializing in psychiatry. There are national guidelines for writing an antidepressant prescription in Finland, although it has been suggested from work done in other countries that practitioners' adherence to these guidelines might be rather poor (de Vries et al. 2016).

The Finnish Drug Purchase Register (DPR) has been advantageous for researchers investigating various diagnosis related medication purchases. However, the published reports have rarely involved a longitudinal perspective of antidepressant use by childhood and YA cancer survivors.

According to the previous reports (Table 2, page 37), female cancer survivors have been reported to have an increased risk for purchasing antidepressants compared with males (Gyllenberg et al. 2011). In a Danish study, males were suggested to have an increased risk for depression as compared with females and childhood cancer survivors' required hospitalizations for a psychiatric disorder more frequently than controls (Lund et al. 2013). In Canadian and Norwegian studies, the risk for CAYAS being prescribed with AD was 20% higher than in controls (Johannsdottir et al. 2017), (Deyell et al. 2013). In a Danish study, the corresponding value was 38% (Lund et al. 2015). A higher risk was found for receiving AD prescriptions in young survivors of CNS, leukemia, hormone-related cancers, as well as in survivors of a group of other malignancies (Khan et al. 2010b), (Deyell et al. 2013), (Johannsdottir et al. 2017), (Lund et al. 2015). In a study of survivors treated with contemporary protocols, all cancer groups were found to elevate the risk for AD use, with age at diagnosis not influencing the outcome (Lund et al. 2015). Convergent results were found also in a Norwegian study (Johannsdottir et al. 2017).

Table 2. Previous literature on cancer survivors' antidepressant purchases.

STUDY	Study design	Period of time	Study population	Control cohort	Outcomes
Increased risk of antidepressant use in childhood cancer survivors: a Danish population-based cohort study (2015) Lund LW et al.	Population-based registry study, retrospective	1975-2009 (1998-2011)	5,452 cancer patients, < 20 years	144, 570, age-matched controls	Higher HRs for AD purchases of CCS
Prescriptions of antidepressants to survivors of cancer in childhood, adolescence and young adulthood- a population-based study (2017) Johannsdottir IM et al.	Population-based registry study, retrospective	1965-2000 (2004-2012)	5,341 cancer survivors, <25 years	14,855, age- and gender matched controls	Higher HRs for AD purchases of CNS, ALL, testicular and other malignancies
Hospital contact for mental disorders in childhood cancer and their siblings in Denmark: a population-based cohort study (2013) Lund LW et al.	Population-based registry study, retrospective	1975-2010	7,088 cancer survivors,	13,105, sibling cohort	Higher HRs for AD use in CNS, solid tumors
Antidepressant use among childhood, adolescent, and young adult cancer: a report of the Childhood, Adolescent and Young Adult Cancer Survivor (CAYACS) Research Program (2013) Deyell RJ et al.	Population-based registry study, retrospective	1970-1995	2,389 5-year cancer survivors	23,890 birth cohort-, gender matched	Likelihood of receiving an AD prescription was higher in cancer survivors, Females and 20 year survivors had increased risk for AD use
Use of Medications for Treating Anxiety and Depression in Cancer Survivors in the United States (2017) Hawkins NA et al.	Population-based, retrospective, Interview survey	2010-2013	3,184 (aged 39-65 years old)	48,181 (similar age group)	Cancer survivors used twice as much medications for anxiety and depression as controls, depression symptoms occurred with cancer related late effects
Consulting and prescribing behavior for anxiety and depression in long-term survivors of cancer in the UK (2010) Khan NF et al	National database survey	2003-2006	26, 213 5 -year cancer survivors, > 30 years	104,486 matched controls	Breast and prostate cancer patients had a higher risk for AD prescriptions compared with controls
Antidepressant therapy in cancer patients: initiation and factors associated with treatment (2015) Pearson SA et al	Insurance data of medication usage, retrospective	2005-2009	5795, > 65 years cancer patients	55,272 matched controls	Cancer patients were more likely to initiate antidepressant medication than controls, although the duration of AD use was shorter in controls

Furthermore, the effectiveness of AD treatment has been discussed in studies conducted earlier, it has been concluded that AD medication might be used in preventing depressive symptoms especially longer-lasting therapy, while in another study, ADs were shown to have a rather insignificant impact on cancer survivors' depressive symptoms (Lund et al. 2015), (Ostuzzi et al. 2015), (Linde et al. 2015). In a study of adult cancer survivors, psychotherapy with or without antidepressant medication was found to be more effective treatment for depression than antidepressants alone ($p<0.05$), although the quality of life of survivors after treatment for depression did not seem to improve (Vyas, Babcock & Kogut 2017).

3 AIMS OF THE STUDY

The purpose of this thesis was to study the late psychosocial effects of childhood and AYA cancer, since the numbers of young age onset cancers are increasing and the need for psychosocial support seems to have risen. Educational-, social and psychiatric outcomes subsequent to childhood and AYA cancer were evaluated. It is anticipated that the data analyzed might be used to plan the future follow-up care of cancer survivors.

The specific aims of the study were:

1. To study educational and vocational achievements and socio-economical outcomes of childhood cancer survivors and population controls.

2. To estimate the current military fitness and the acceptance rate of male cancer patients for the compulsory military service in Finland, as well as examining conscript survivors' performance in physical and cognitive tests in military service as compared with population controls.

3. To investigate the risk of psychiatric morbidity following cancer treatment within a nationwide 5-year survivor cohort of patients diagnosed with cancer before the age of 35 years as compared with a sibling cohort.

4. To evaluate the frequencies and risk for antidepressant purchases of childhood and AYA cancer patients and their siblings.

4 SUBJECTS AND METHODS

4.1 Study subjects

4.1.1 Cancer patients and controls

In these population-based studies, various outcome measures of cancer patients were evaluated. In studies I and II, the cohort examined consisted of childhood cancer survivors for whom, data on five age-, sex- and place of residence matched population controls were retrieved. In study III, 5-year survivors of childhood and young adult (YA) cancers survivors and their sibling cohorts were assessed. In study IV, cancer patients diagnosed below the age of 35 years between 1993 and 2004 and their siblings with the same range of birth years were evaluated (Figure 6).

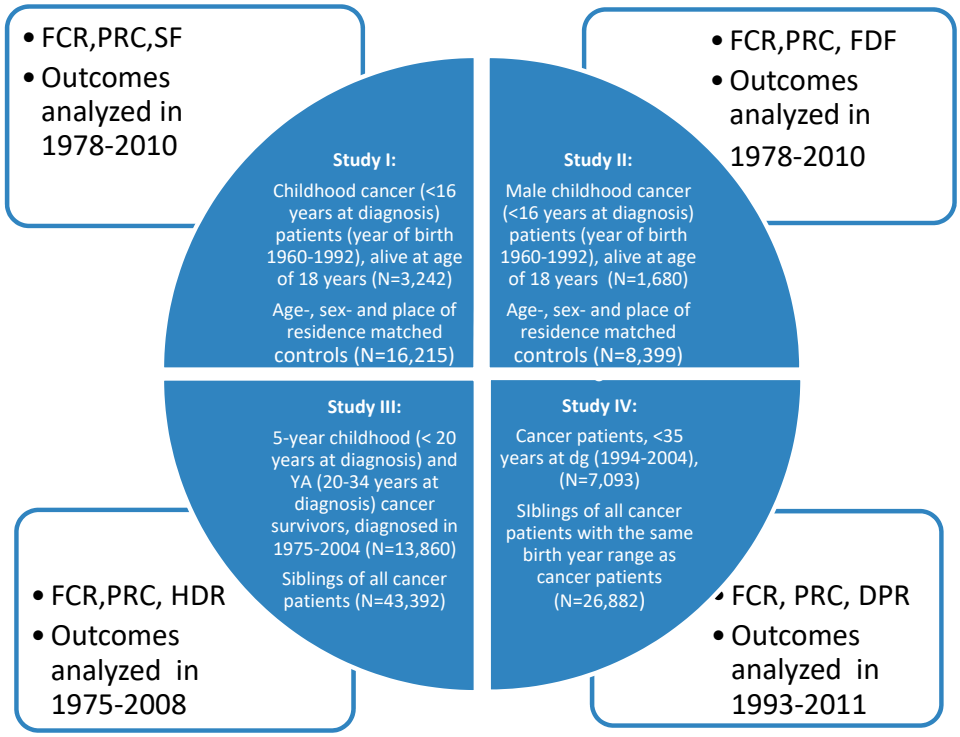


Figure 6. The description of study populations and data sources. FCR=the Finnish Cancer Register, PRC=the Population Register Centre, DPR=the Drug Purchase Register, FDF=the Finnish Defence Forces, HDR=the Hospital Discharge Register, SF=the Statistics Finland, SII=the Social Insurance Institution Register (KELA).

Study I:

Study I investigated educational and social outcomes; the inclusion criteria were as follows: age under 16 years at cancer diagnosis, the year of birth from 1960 to 1992, and being alive in the year of 18th birthday. Inclusion criteria were fulfilled by 3242 survivors of childhood cancer. The data collected by the end of 2010 were gathered from the FCR. To compare educational and social outcomes with the control population, five age-, sex- and place of residence matched controls were retrieved from the PRC. Since it was intended to study the effect of parents' socioeconomical status, the identification of data about the parents of both study groups were gathered from the PRC.

Study II:

In study II, the aim was to study current acceptance rates of childhood cancer survivors for military service and additionally their military fitness was compared to healthy controls. To achieve that goal, all males diagnosed with cancer before the age of 16 years, who were born between 1960 and 1992 and were alive on their 18th birthday, were identified using the Finnish Cancer Register (FCR) at the end of 2010. The inclusion criteria were met by 1680 cancer patients. Similarly to study I, data on five age-, sex- and place of residence matched controls were retrieved from the PRC. A total of 8399 controls met the inclusion criteria.

Each Finnish male citizen receives a call-up to compulsory military service during the year he turns 18 years of age. It is noteworthy, that previously only males could participate in military service and it should also be mentioned that before the 1990s, most cancer survivors were exempted from military service. The physical and cognitive test results during military service of both cohorts, were retrieved from the FDF, although some of the cognitive test results are strictly confidential due to the rules of Finnish Defence Forces and were not available. Register linkage of these databases was conducted by the research unit of the FDF.

Study III:

The aim of study III was to study psychiatric morbidity of childhood and young adult cancer survivors and to compare it with siblings. The study population cancer patients diagnosed between 1.1.1975 and 31.12.2004, surviving at least 5 years and not having a diagnosis of a second malignancy within the 5-year survival. They were identified from the FCR. A total of 13,860 cancer patients fulfilled the inclusion criteria. Healthy siblings (without cancer at a young age) of the patient cohort, were identified (N=43,392) by linkage to the PRC. Data on psychiatric diagnoses were retrieved from the HDR.

Study IV:

In study IV, the aim was to study the cumulative incidence of first post cancer diagnosis purchases of antidepressant medication in childhood and YA cancer patients. A total of 7 093 cancer patients diagnosed before the age of 35 years, during 1994-2004 were identified from the FCR and a total of 26 882 sibling controls with the same range of birth years from the PRC. The data on medication purchases of these groups since 1.1.1993 were retrieved from the Drug Purchase Register (DPR) kept by the Social Insurance Institution of Finland (SII).

4.2 Registries used in studies I-IV

4.2.1 The registries from which the study cohorts were identified

The Population Register Centre (PRC) and regional register offices maintain the Finnish Population Information System. This register contains a unique personal identification code (PIC) for each Finnish citizen born in 1967 and thereafter. In addition, individual data gathered by the system includes name, address, citizenship and native language, family relations (also links to parents, and siblings born after 1955) and date of birth and death (if data is applicable). The register has been computerized since 1971 and this data can be used for various study projects and it offers also the possibility to undertake linkages.

The Finnish Cancer Registry (FCR) is a population-based, nationwide register, which contains information on all Finnish cancer cases since 1953. From 1961 it has been compulsory for physicians, hospitals and pathologists to report every new cancer case; this is an obligation defined in a national laws. The FCR contains data on cancer patients including date and stage of cancer diagnosis, the primary site of the tumor, its malignancy and cell type, primary treatment details of surgery, chemotherapy and radiotherapy, and date and cause of possible death (Figure 7, page 44). As information on cancer-related deaths (death certificates) are annually reported by Statistics Finland, FCR data coverage is nearly complete (90-100%) (Leinonen et al. 2017), (Teppo, Pukkala & Lehtonen 1994).

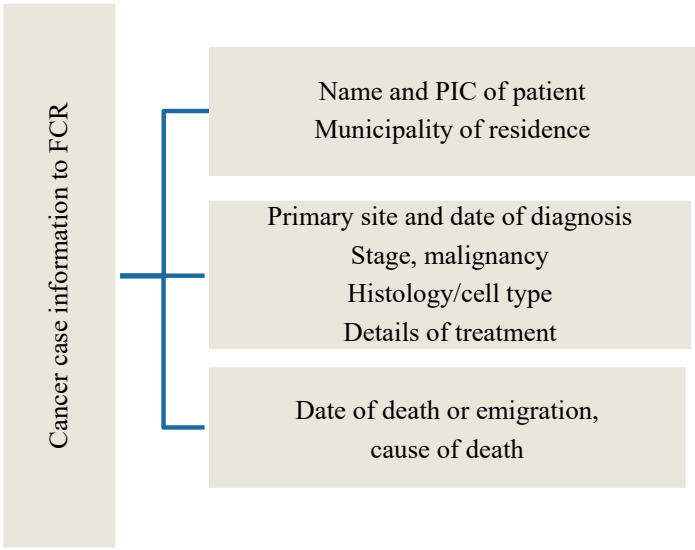


Figure 7. The data gathered into the Finnish Cancer Register (FCR).

4.2.2 The registries from which the study outcomes were collected

The data on all hospitalizations in Finland from 1969 have been included in the Finnish Hospital Discharge Register (HDR) and data have been available in electronic format since 1.1.1975. The HDR contains data gathered from both private sector and public health care providers including the following information: the date of admission and discharge, main diagnoses for treatment (International Codes of Diseases, ICD codes), data on treatment procedures, and data on treatment related further services. Additionally, from 1994, all out-patient visits to specialized care units have been registered. In Finland, cancer treatments are mainly performed in public health care, with the costs subsidized by the Finnish national health care system. For research purposes cancer survivors can be linked to the HDR by using the PIC. The ICD codes for psychiatric outcomes were retrieved from the HDR and ICD -8 and -9 codes were manually converted to ICD 10 diagnostic codes (study III).

The Social Insurance Institution (SII) maintains the Drug Purchase Register (DPR) and data on prescription drug purchases have been available since 1993. This register contains information of all prescription refundable medications (not the over-the-counter medications), and drugs utilized in various health care institutions for treatment and research purposes. The drugs are classified according to the Anatomical Therapeutic Chemical (ATC) codes maintained by the World Health

Organization (WHO). The register files contain the patients' PIC, the price and the package size of the drug, and the date of the purchasing of the drug. In study IV, the data on the first purchase of antidepressants after the cancer diagnosis (or for the siblings) were collected as a measure of an adverse effects of the cancer.

The Finnish Defence Forces (FDF) has stored the information concerning conscripts' military classification, physical, cognitive, and leadership skills, and military training also in electronic form, but the exact time periods are not available publicly, even to researchers. Only the data linkages are provided after specific research permission. The database contains the following information: the data on conscripts' enlistment, physical ability test results (maximal aerobic endurance evaluated by a 12-minute running test (Cooper test)), and musculoskeletal capacity (maximal muscular strength by measuring the result of a standing long jump), evaluation of bodily dynamic endurance (measured by sit-ups), and static endurance of body muscles (measurement of muscle strength of upper extremities and back) and data on total fitness index. The data includes also information of conscripts' basic ability as assessed in two tests. The data profile of test 1 is available, but basic ability test 2 contains data on conscripts' leadership skills, which makes them confidential, non-available information. Furthermore, the database provides information on conscripts' educational level and reasons for exemption.

Statistics Finland (SF) has been established in 1865 and it has been built merely for statistical purposes. Its databases provide national data based on public records, interview studies, and questionnaire-based surveys. Since the 1980s the SF has collected annual statistical data at the end of comprehensive education containing data on the numbers of pupils in each year-class, number of pupils having received comprehensive school certificates, and the number of pupils having failed to progress to the next class. In addition, the grades of the qualification diploma at the end of comprehensive school are recorded (mother tongue, first foreign language, mathematics and sports). The statistics on comprehensive and upper secondary schools are based on total data collected via a web-based questionnaire. Additionally, data on yearly income were retrieved from the SF.

The Social Insurance Institution Register (SII) of Finland (KELA) collects statistical information of unemployment benefit recipients, payment durations and expenditures. The gender, municipality and age of each unemployment benefit receiver are gathered in collaboration with Statistics Finland. A person may join a voluntary unemployment benefit society, and obtain earnings-related benefits, when unemployed, otherwise KELA provides a basic unemployment allowance to all other unemployed persons. To be eligible for this benefit, a person has an obligation to register to the Employment and Economic Development Office. The pension benefit also is a part of the Finnish social security system and KELA pays the national pensions, and additionally the

individual may receive an earnings-related pension. KELA collects data on unemployment and retirement in collaboration with the PRC, Statistics Finland and the Tax Administration of Finland. The information includes age, gender, benefit status and data on employment.

4.3 Methods

4.3.1 Gathering and integration of the registry-based data

Study I:

When studying educational attainments of cancer survivors in comparison to controls, grades from graduation diploma of comprehensive school and detailed information on subjects' further education were gathered from Statistics Finland. In addition, data from Statistics Finland were analyzed, when evaluating the social effects of survivors, their employment, retirement, and yearly income status. A description of the educational system in Finland is shown in Figure 8.

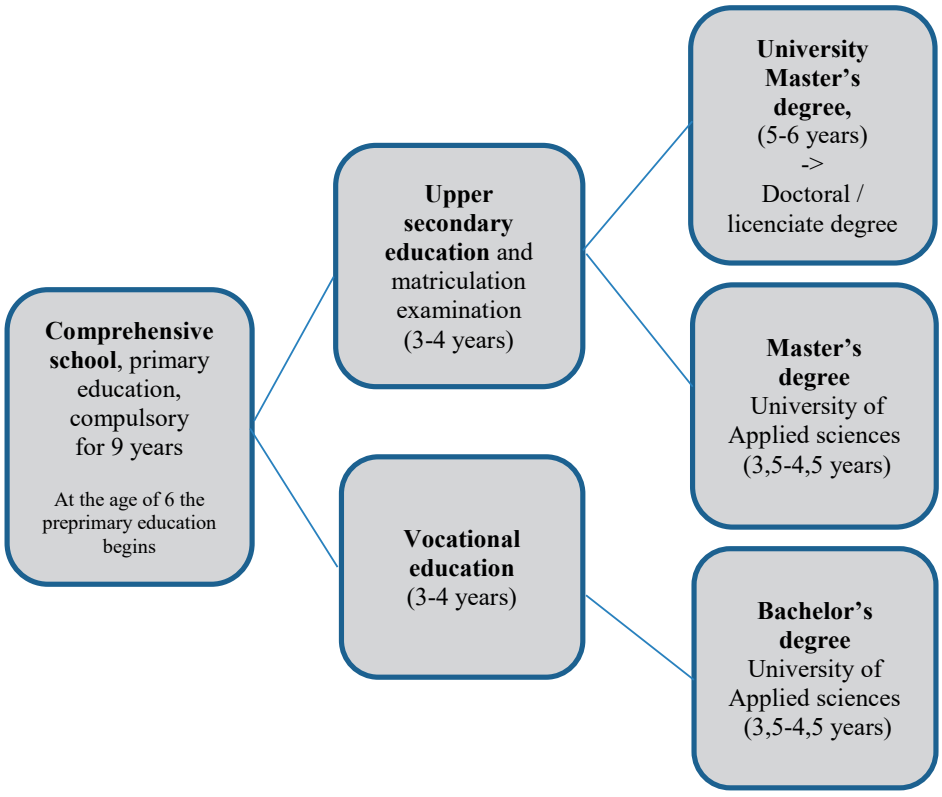


Figure 8. The description of the educational system of Finland (modified from study I)**.**

Study II:

In study II, our aim was to study male survivors' and their controls' physical and cognitive performance while they were undertaking Finnish military service. Previously the majority of childhood and adolescent cancer survivors have been exempted from military service. Nowadays, cancer survivors with no or only minor physical late effects usually are categorized to fitness categories A or B. Enlisted conscripts perform tests measuring their physical capacity during the first weeks of their service (Figure 9). Maximal aerobic capacity is measured with twelve minutes running test (Cooper test), musculoskeletal capacity is tested by a standing long jump (maximal muscular strength), sit-ups (body's flexor muscles, dynamic endurance evaluation) and push-ups (static endurance of body muscles, dynamic muscle strength of upper extremities) and additionally with a back muscle test. An individual's overall fitness index is calculated from these results evaluating both aerobic and muscular fitness (Cooper 1968). In addition to physical performance testing, the cognitive capacity of the conscript is examined, but some of these test results are strictly confidential according to the rules of Finnish Defence Forces.

Required data for these analyses were gathered from FCR, PRC and linked to the conscripts' results from FDF. In addition, we analyzed military enlistment frequency, delay and reasons for exemption of the cancer survivors compared to that of healthy controls. Call-up, enlistment and the testing protocol of Finnish military service are shown in Figure 9.

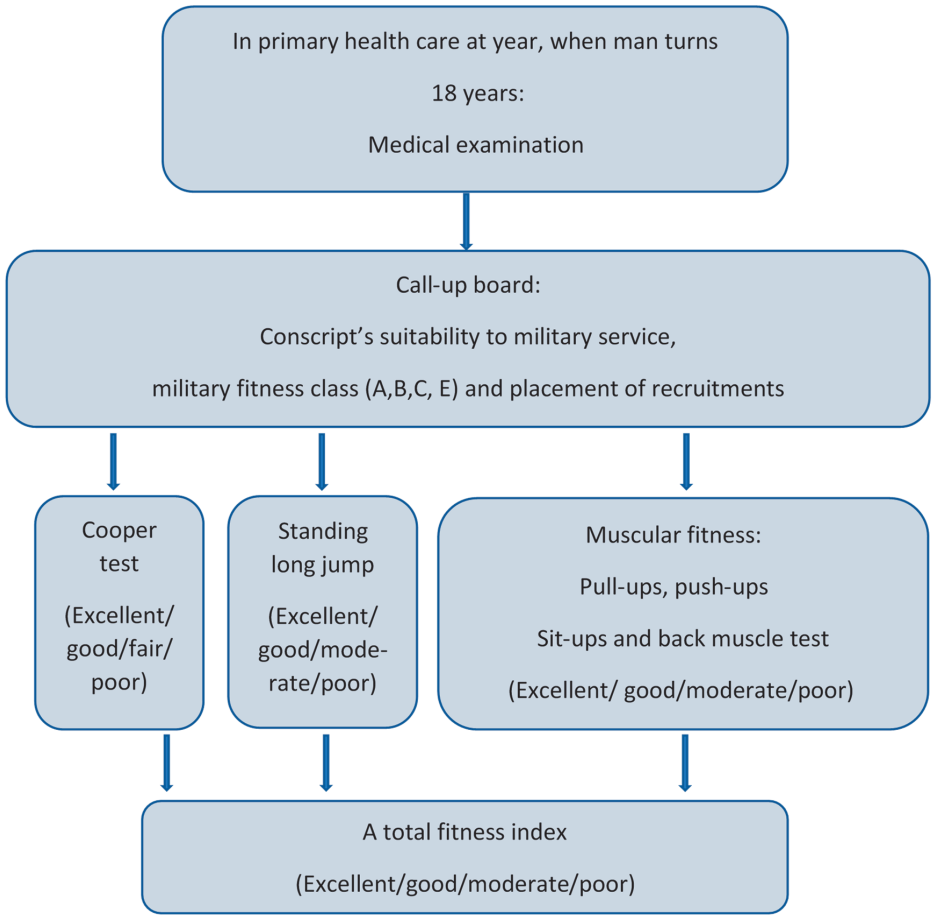


Figure 9. The military service call-up, enlistment and physical fitness test procedures in Finland.

Study III:

The cancer survivors evaluated in study III were divided into groups, which consisted of childhood and adolescent survivors (0-19 years old at cancer diagnosis) and young adult (20-34 years at cancer diagnosis) survivors. This division was made to simplify the analyzing process, as there are differences in cancer type distribution and treatment protocols in these groups. In order to obtain comparative data analysis on psychiatric outcomes; siblings and half siblings were identified from PRC by using their personal PIC and five-year survivor data were gathered from FCR. In order to be able to study hospitalizations attributable to psychiatric disorders in survivors and siblings, registry data from HDR were gathered after identifying and linking data from FCR and PRC. The subjects' data were linked to the HDR by using the PIC. The International Classification of

Diseases (ICD) codes for mental health disorders were used in outcome analyses and diagnoses were retrieved from the HDR. These data have been available electronically since January 1st1975. In order to obtain analyzable data, the previously used diagnosis codes ICD-8 during 1969- 1986 and ICD-9 during 1987-1995, were manually converted into the ICD 10 format.

Study IV:

In study IV, the cumulative incidence of first purchases of antidepressant medications (ATC-group N06A) were analyzed from the data on SII and DPR between January 1st 1994 and December 31st 2011 at the latest. Anatomical Therapeutic Chemical (ATC) codes by the World Health Organization (WHO) classify all of the drugs (Table 3).

Table 3. The Anatomical Therapeutic Chemical (ATC) codes for the antidepressants evaluated in Study IV.

ATC-CODE	MEDICINE GROUP
N06A	Antidepressants
N06AA	Non-selective monoamine reuptake inhibitors
N06AB	Selective serotonin reuptake inhibitors
N06AG	Monoamine oxidase A inhibitors
N06AX	Other antidepressants

4.4 Statistical analyses

Study I:

A conditional logistic regression analysis was used to analyze survivors' educational attainments in comparison to their age-and sex-matched controls. The GEE-method (generalized estimating equation) was used in the analysis of ordinal response variables, and income level analysis. In the outcome analysis, also a random effect for continuous variables was taken into account with mixed method models. In addition, parental education level has been claimed to have a major influence on the results of offspring and thus this variable has been controlled for in all analyses.

When analyzing, if early age onset cancer exerted any effects on educational attainments and income level of the survivors, the data were adjusted for parental education, year of birth, gender and age. With statistical analysis by logistic

regression model, we studied the association between background variables and binary response variables. Furthermore, linear models were used to analyze the effects of parental education and year of birth on the income level of study subjects.

Study II:

In study II, conditional logistic regression analysis was performed to analyze physical and cognitive outcomes of enlisted cancer survivors and controls. Prior to this analysis, dichotomous response variables were identified and included in the analysis.

To analyze hazard ratios (HR) and 95% confidence intervals (CI) of the data, register linkages by FDF, FCR and PRC were performed. We categorized the data according to the time of diagnosis in an attempt to detect possible changes with the passage of time, by dividing the leukemia/NHL group based on time points of changing treatment protocols (before 1992, 1992-2001, after 2001) and before 1990, 1990-1999, after 1999 in other cancer groups.

The GEE-method with the cumulative logit link function for ordinal response variables, and mixed models with the matching group as a random effect for continuous variables were used. Among the survivors, the associations between two nominal variables were studied by using the chi-square test, between ordinal and nominal variables using the chi-square test for trend, and between nominal and continuous variables using a one-way analysis of variance.

In **study III**, the five-year survivors' risk for a new psychiatric diagnosis was compared to siblings' outcomes. The risk assessment of various outcomes was made by Cox proportional hazard models, with calendar age as the time variable. In addition, cancer, birth decade, gender, and interaction between gender and cancer, were used as predictor variables, while hazard ratios (HR) and 95% confidence intervals for each of the psychiatric outcomes were calculated by Cox proportional models. To analyze, whether there would be differences in these outcomes attributable to time, we used each treatment era (1975-1982, 1983-1992, 1993-2004), as a predictor in assessing these data. Furthermore, the diagnostic era was used as a proxy for changes in treatment regimen and possible societal changes. Since radiotherapy had been used in the treatment of BT-, leukemia and NHL-, radiotherapy was used as a dichotomous variable (YES/NO), to analyze its possible effects on psychiatric outcomes.

To take into account differences in the distribution of diagnoses, treatment regimens and programs and because survivors might have dissimilar vulnerabilities to adverse psychiatric outcomes, diagnostic age groups were

divided into two (childhood (0-19 years at cancer diagnosis) and young adult patients, YA (20-34 years at cancer diagnosis)).

The incidence of psychiatric late effects was studied by using International Classification of Diseases (ICD) codes for psychiatric diagnoses. The main psychiatric diagnoses collected from the HDR were categorized as follows: organic memory and brain disorders (F0), alcohol/drug abuse (F1), schizophrenia and other psychotic disorders (F2), mood disorders (F3), neurotic/anxiety disorders (F4), somatization/eating disorders (F5) and personality disorders (F6). The computerized sampling of diagnostic codes was retrieved from the hospital discharge register (HDR).

In study IV, the Cox regression models with calendar age as a time variable were used in assessing the risk (HR) for first time antidepressant purchases in patients diagnosed with cancer in childhood or in young adulthood compared with sibling controls. Univariate models included group (cancer patients or controls) as a predictor variable and multivariable models included group, gender and interaction between group and gender as the predictor variable. Additional analyses with diagnosis (leukemia, lymphoma, CNS malignancies, sarcomas, and other malignancies) or diagnosis and gender as a predictor variable were performed.

The cumulative incidence plot was based on two subgroups: one comprising patients diagnosed between 0 and 19 years of age and siblings starting from birth, and the other comprising patients aged between 20 and 34 years at cancer diagnosis and siblings starting from the age of 20 years. The models were adjusted for gender.

To analyze for a possible trend in time (before and after the year 2000) for AD medication purchases, HRs for AD purchases were calculated separately for each group.

In all studies, statistical data were analyzed using the software SAS for Windows version 9.4, and P-values below 0.05 were considered statistically significant.

4.5 Ethics

Permits for registry linkages were obtained from the Finnish Ministry of Social Affairs and Health (THL/62/5.05.00/2011 for studies I and II; STM/980/2006 for study III; THL/1184/5.05.00/2011 for study IV),the CPR (Dnro 145/410/11, 18.8.2011) , the FDF (AI1702, 26.1.2012), Statistics Finland (THL / TK53-95-11), and SII (Kela 28/522/2012).The study protocol was approved by the clinical research center of the South-West Finland Hospital District (T19/2013, 28.1.2013). Registry-based studies do not require a separate ethical board evaluation.

5 RESULTS

5.1 Educational and social outcomes after young age onset cancer

5.1.1 Cognitive performance and educational attainments of the survivors

When the data on four main subjects (mother tongue, mathematics, first foreign language, and sports) at the end of comprehensive school in childhood cancer survivors and reference group were examined, we found that BT survivors had lower grades than controls in all analyzed school subjects. A similar result was found in leukemia-/NHL survivors, but ST survivors had lower grades only in sports, when compared with controls. The proportion of those sitting the national matriculation examination was lower in BT, and leukemia-/NHL survivors, while ST survivors completed this educational step similarly to controls. Younger age (< 7 years) at diagnosis in the BT group and cranial irradiation, treatment received within the last era of this study (patients treated after 1992), and adolescence (>12 years) in leukemia/NHL survivors, were associated with non-graduation from further education (Table 4).

Table 4. Grades of the four main subjects at the end of comprehensive school and the proportions of study subjects finalizing matriculation examination at the end of upper secondary school. *=male gender was associated with poorer outcomes, a=age below 7 years at diagnosis was associated with poorer outcomes, b=received irradiation was associated with poorer outcomes.

	Mother tongue	*p*	Sports	*p*	First foreign language	*p*	Mathematics	*p*	Matriculation examination N (%)	*p*
Survivors of brain tumors										
Controls (N= 3960)	7.7 (1.2)	0.023 *	8.2 (1.1)	<0.001 ab	7.5 (1.4)	<0.001*ab	7.4 (1.4)	<0.001 a	1735 (43.8)	<0.001*ab
Survivors (N= 792)	7.6 (1.2)		7.8 (1.0)		7.2 (1.3)		7.2 (1.3)		236 (27.3)	
Survivors of solid tumors										
Controls (N=7249)	7.8 (1.2)	0.73*	8.2 (1.1)	<0.001	7.6 (1.4)	0.25*	7.5 (1.4)	0.37*	3316 (45.7)	0.073*
Survivors (N=1450)	7.8 (1.8)		8.0 (1.0)		7.5 (1.4)		7.4 (1.4)		629 (43.4)	
Survivors of leukemia/NHL										
Controls (N= 5005)	7.7 (1.2)	0.08*b	8.2 (1.0)	<0.001 b	7.5 (1.4)	0.001*a	7.4 (1.4)	0.049	2230 (44.6)	<0.001*b
Survivors (N=1001)	7.6 (1.2)		7.9 (1.0)		7.3 (1.4)		7.3 (1.4)		360 (36.0)	

Childhood cancer survivors' further educational level was examined by comparing their results to that of controls. The data on the results of the national matriculation examination were also analyzed. We found BT survivors were less likely to complete the matriculation examination than controls (27.3% vs 43.8%). When subdivided by gender, age and therapy-related aspects of cognitive performance, we found that in particular, younger males (<7 years) at the diagnosis with BT, and those treated with cranial radiation therapy had the poorest results, especially in the first foreign language and in the final results in their matriculation examination. Overall, childhood cancer survivors had a higher risk for not completing any further education after the comprehensive school, as the proportion of those with no further schooling was higher in survivors than in controls in all diagnosis groups (Table 5).

Table 5. Educational level of main cancer groups of childhood cancer survivors and their controls at the end of comprehensive school. Modified from Study I, Table 4.

	BT survivors/ controls	***p***	**ST survivors/ controls**	***p***	**Leukemia/NHL survivors/ controls**	***p***
	N (%)		**N (%)**		**N (%)**	
No graduation	265/910 (33.5/23.0)	<0.001	362/1550 (25.0/21.4)	0.02	254/1154 (29.2/23.1)	<0.001
Upper secondary	391/2022 (49.4/51.1)		686/3662 (47.3/50.5)		506/2536 (50.6/50.7)	
Low degree level	104/689 (13.1/17.4)		255/1327 (17.6/18.3)		149/869 (14.9/17.4)	
High degree level	31/391 (3.9/8.1)		141/672 (9.7/9.3)		50/416 (5.0/8.3)	
Doctorate or equivalent level	1/20 (0.1/0.5)		6/38 (0.4/0.5)		4/30 (0.4/0.6)	

The Finnish educational system is explained in Figure 8, page 47.

The cognitive performance of male childhood cancer survivors was also assessed during military service by analyzing the data on visuospatial, verbal, and arithmetic skills (study II). The basic ability test (basic ability test P1) measures the conscripts' general learning capacity. BT survivors seemed to have poorer outcomes in all tested cognitive skills and it is notable that also non-irradiated survivors had significantly poorer performance in all of the tested categories. However, enlisted leukemia/NHL survivors seemed to have a cognitive performance comparable to controls. The cognitive test outcomes are presented in Table 6.

Table 6. Cognitive tests in BT and leukemia/NHL survivors and their controls in military service, outcome assessment also according irradiation status. Table modified from Study II, Table 5.

Cognitive tests	Brain tumor survivors and their controls			Leukemia/ NHL survivors and their controls		
	survivors N = 45	controls N = 592	*p*-value	survivors N = 88	controls N = 757	*p*-value
	mean (SD)	mean (SD)		mean (SD)	mean (SD)	
General talent	3.82 (1.59)	4.80 (1.89)	<0.01	4.76 (1.88)	4.80 (1.85)	0.88
Mathematical	3.96 (1.61)	4.71 (1.90)	<0.01	4.95 (2.09)	5.04 (1.98)	0.72
Verbal	3.67 (1.72)	4.62 (1.94)	<0.01	4.72 (1.92)	4.62 (1.83)	0.64
Visual	4.20 (1.88)	5.05 (2.03)	<0.01	4.67 (1.97)	4.72 (1.95)	0.82
	Irradiated brain tumors			**Irradiated leukemias**		
	survivors N = 7	controls N =192	*p*-value	survivors N = 12	controls N = 194	*p*-value
General talent	3.43 (1.27)	4.79 (1.90)	0.06	4.17 (2.55)	4.97 (1.89)	0.15
Mathematical	3.71 (1.60)	4.61 (2.04)	0.25	4.00 (2.49)	4.72 (1.84)	0.20
Verbal	3.86 (1.68)	4.68 (1.88)	0.25	4.33 (1.87)	4.86 (1.93)	0.36
Visual	3.43 (1.62)	5.07 (1.97)	0.03	4.50 (3.00)	5.30 (1.97)	0.13

5.1.2 Employment and retirement of the survivors

In the assessment of social outcomes after childhood cancer, we analyzed the data on employment, and retirement status of childhood cancer survivors and controls. The effect of cancer survivorship on economical outcomes, was evaluated by searching the data on the study subjects' income level. In the available data, no elevations in the risk for unemployment was found either in BT- (p=0.27), ST- (p=0.85) or leukemia/NHL survivors (p=0.26) in comparison to controls. It is notable that BT survivors were found to have a nearly 15- fold risk for early retirement in comparison to controls, the corresponding values were 2-fold for ST-survivors and 4-fold for leukemia/NHL survivors. The retirement was associated with cancer survivors' earlier treatment era (before 1990s) and younger age at the diagnosis. In particular, leukemia/NHL survivors treated after the year 1992 were found to have a lower risk for early retirement (OR 0.6, 95% CI 0.2 – 0.9) in comparison with those treated earlier (table 7, page 57).

In the analysis of income level, we found that survivors had a lower income level, consistently in all survivor groups compared with controls, with the exception for male ST survivors. An assessment of both parental education and survivors' income level was additionally performed; their parents' higher education level was associated with a higher income level in the survivors.

Table 7. Socio-economical status of childhood cancer survivors.

Survivors of brain tumors	**Survivors (N=712) / Controls (N=3868)**	**Male Gender**	**Age below 7 y at dg**	**Era of treatment (before 1990ies)**	**No irradiation**
Unemployment					
OR (95%CI)	1.2 (0.9-1.5)	2.4 (1.4-4.2)	1.7 (0.9-3.3)	4.1 (1.4-11.7)	0.7 (0.4-1.1)
Retirement					
OR (95% CI)	14.8 (10.4-21.0)	0.9 (0.6-1.4)	2.1 (1.3-3.6)	5.2 (1.8-15.2)	0.4 (0.2-0.5)
Survivors of solid tumors	**Survivors (N=1341) / Controls (N=7037)**	**Male Gender**	**Age below 7 y at dg**	**Era of treatment (before 1990ies)**	**No irradiation**
Unemployment	1.0 (0.8-1.3)	1.3 (0.9-2.0)	0.9 (0.6-1.5)	0.9 (0.5-1.7)	0.9 (0.6-1.4)
OR (95%CI)					
Retirement	2.2 (1.5-3.0)	1.2 (0.7-2.1)	1.2 (0.6-2.3)	1.9 (0.6-6.1)	1.5 (0.8-2.7)
OR (95% CI)					
Survivors of leukemia/NHL	**Survivors (N=923) / Controls (N=4897)**	**Male Gender**	**Age below 7 y at dg**	**Era of treatment (before 1990ies)**	**No irradiation**
Unemployment	1.2 (0.9-1.5)	1.2 (0.8-2.0)	1.5 (0.8-2.9)	0.8 (0.4-1.4)	1.2 (0.7-2.0)
OR (95%CI)					
Retirement	4.0 (2.8-5.8)	0.6 (0.3-0.9)	2.6 (1.0-6.3)	0.6(0.2-0.9)	1.3 (0.7-2.3)
OR (95% CI)					

5.2 Physical outcomes of males in military service after young age onset cancer

5.2.1 Male survivors' physical performance measured in compulsory military service

The aim of study II was to study whether the exemption rate of childhood cancer survivors had changed since 1990. Data-analysis revealed no change, i.e. among survivors, the exemption rate was found to be consistently higher than in controls (45.6% and 8.1%, respectively, $p < 0.001$). An analysis of reasons leading to exemption was performed, see Table 8.

Table 8. Reasons for exemption of childhood cancer survivors and their controls from the Finnish military service, modified from Study II, table 1. *=cancer diagnosed at call-up age. The total number of evaluable survivors was 1300, and a total of controls was 7209, the number of exempted men was 593 and 562, respectively.

REASONS FOR EXEMPTION/DELAY			
SURVIVORS		CONTROLS	
Cancer	53.8%	Psychiatric disorder	47.6%
Psychiatric disorder	6.9%	Unknown/not reported	10.4%
Neurologic disease	6.6%	Endocrinologic disease	7.0%
Unknown/not reported	6.1%	Neurologic disease	5.9%
Endocrinologic disease	5.5%	Respiratory disease	5.4%
Musculoskeletal/con-		Injury/Intoxication/	
nective tissue disease	3.1%	hematological disease	4.7%
Injury/Intoxication/		Musculoskeletal/connect.	4.5%
hematological disease	2.5%	Congenital malform./	
Congenital malform./		chromosomal abnorm.	4.5%
chromosomal abnormality	2.3%	Gastrointestinal disease	3.1%
Ocular disease	1.7%	Dermal disease	2.5%
Circulatory disease	1.1%	Ear disease	1.4%
Gastrointestinal disease	0.8%	Ocular disease	1.3%
Ear disease	0.6%	Urogenital disease	1.3%
Respiratory disease	0.6%	Circulatory disease	1.3%
Dermal disease	0.5%	Infectious disease	0.2%
Infectious disease	0.3%	Cancer*	0.2%

The physical fitness outcomes of male childhood cancer survivors in military service were assessed by analyzing the results obtained in the Cooper running test and muscular fitness. The performance of both leukemia/NHL and BT survivors was poorer than controls (Table 9). A total fitness index was also calculated. BT survivors were found to have poorer results than controls. By analyzing the data on the separate muscle strength tests (pull-ups, push-ups, sit-ups, and back muscle test), we found that the results did not differ significantly from those of controls in any of the three survivor groups. However, leukemia/NHL ($p<0.001$), solid tumor ($p=0.005$), and BT ($p=0.001$) survivors had significantly worse results in the standing long jump than their controls. Suprisingly, we found that irradiation did not seem be the cause for the poorer results.

Table 9. Physical performance test results of main cancer group survivors and their controls at the beginning of military service, (Modified from Study II).

Test	Solid tumor survivors and their controls			Brain tumor survivors and their controls			Leukemia/ NHL survivors and their controls		
	survivor **N (%)**	control **N (%)**	***p*-value**	survivor **N (%)**	control **N (%)**	***p*-value**	survivor **N (%)**	control **N (%)**	***p*-value**
Fitness index			0.24			<0.05			0.14
Excellent	20 (8 %)	242 (10 %)		6 (8 %)	92 (10 %)		13 (8 %)	112 (9 %)	
Good	87 (33 %)	851 (34 %)		18 (24 %)	310 (32 %)		49 (30 %)	443 (34 %)	
Moderate	97 (37 %)	952 (38 %)		30 (40 %)	378 (39 %)		68 (41 %)	510 (39 %)	
Poor	57 (22 %)	478 (18 %)		21 (28 %)	186 (19 %)		35 (21 %)	276 (18 %)	
Cooper test			0.18			0.01			0.03
Excellent (>3000m)	19 (7 %)	229 (9 %)		5 (7 %)	85 (9 %)		8 (5 %)	111 (9 %)	
Good (>2600m)	81 (32 %)	811 (32 %)		19 (25 %)	307 (32 %)		45 (27 %)	417 (32 %)	
Fair (>2200m)	101 (39 %)	1029 (41 %)		25 (33 %)	394 (40 %)		84 (50 %)	561 (43 %)	
Poor (<2000m)	57 (22 %)	459 (18 %)		26 (35 %)	183 (19 %)		30 (18 %)	206 (16 %)	
Muscle fitness			0.19			0.02			0.05
Excellent	36 (13 %)	350 (14 %)		7 (9 %)	142 (15 %)		22 (13 %)	175 (13 %)	
Good	70 (26 %)	763 (30 %)		15 (20 %)	273 (28 %)		35 (21 %)	394 (30 %)	
Moderate	84 (32 %)	777 (31 %)		27 (36 %)	289 (30 %)		63 (38 %)	420 (33 %)	
Poor	76 (29 %)	635 (25 %)		26 (35 %)	265 (27 %)		46 (28 %)	305 (%)	

5.3 Psychiatric outcomes after young age onset cancer

5.3.1 Analysis of psychiatric morbidity by linkage to the Hospital discharge register (HDR)

The observations on the psychiatric outcomes were made by dividing study cohorts by age (age groups 0-19 years and 20-34 years), gender and treatment era. Elevated HRs for organic memory and brain disorders were found both after childhood (HR 4.9; 95%CI 2.7-8.9) and YA cancers (HR 2.1; 95%CI 1.4-3.1). Young age onset cancer survivors were commonly affected by mood disorders, both in childhood (HR 1.3; 95% CI 1.1-1.7) and young adulthood (1.3; 95%CI 1.1-1.5) compared with siblings (Table 10). Furthermore, in the subgroup analysis, the risk for mood disorders was elevated in survivors of childhood ALL (HR 2.4; 95% CI 1.4-4.1), HL (HR 2.3; 95% CI 1.4-4.7), and BT survivors (HR 4.1; 95% CI 2.9-5.9) as well as in YA age group among NHL (HR 1.8; 95% CI 1.1-3.0), HL (HR 1.8; 95% CI 1.1-3.0), and CNS malignancies (HR 1.8; 95% CI 1.2-2.6). The more detailed outcome measures are presented in Table 10.

Female survivors were observed to have significantly higher HRs for several psychiatric outcomes in both age groups. In particular, female survivors were detected to have a pronounced risk for neurotic/anxiety disorders (childhood, $p<0.001$ and YA, $p<0.03$), and this finding was consistent, when compared with male survivors and siblings. Childhood cancer survivors were found to display a susceptibility towards psychotic and somatic/eating disorders. In the analysis of cancer survivors' risk for alcohol/drug abuse, we found that these individuals did not exhibit any significantly elevated risk, but it was notable that YA female survivors showed a trend towards an elevated risk and in the subgroup analysis, the survivors of YA testicular malignancies had higher HRs for this outcome as compared with their siblings (Table 11).

Table 10. Risk assessment (hazard ratio, HR) of studied psychiatric outcomes subdivided by gender, age group, and treatment era.

Treatment era, gender and age group	Organic memory/brain disorder	Alcohol/drug abuse related	Psychotic disorders	Mood disorders	Neurotic disorders	Personality disorders	Somatization and eating disorders
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
N=0-19 aged, total	**N=19**	**N=59**	**N=56**	**N=101**	**N=84**	**N=16**	**N=48**
Males 0-19 years							
1975-1984	5.2	0.6	1.0	1.4	0.9	0.8	0.6
	(2.2-12.2)	(0.4-1.0)	(0.6-1.8)	(1.0-2.1)	(0.6-1.4)	(0.4-1.4)	(0.2-2.2)
1985-1994	5.1	1.1	1.0	1.3	0.8	1.0	0.8
	(2.0-13.3)	(0.7-1.6)	(0.6-1.8)	(0.9-1.9)	(0.5-1.3)	(0.6-1.9)	(0.3-2.3)
1995-2004	7.0	0.5	1.0	0.8	0.8	0.4	0.0
	(1.8-27.6)	(0.2-1.2)	(0.5-2.4)	(0.4-1.5)	(0.4-1.6)	(0.1-0.7)	(0.0-0.0)
Females 0-19 years							
1975-1984	4.4	0.9	1.9	1.6	2.1	2.3	2.1
	(1.7-11.6)	(0.5-1.6)	(1.2-3.0)	(1.1-2.3)	(1.4-3.1)	(1.4-3.8)	(0.8-5.5)
1985-1994	4.4	1.6	1.9	1.5	1.9	2.8	2.7
	(1.5-12.7)	(1.0-2.8)	(1.1-3.0)	(1.1-2.1)	(1.2-2.9)	(1.7-4.6)	(1.3-5.4)
1995-2004	5.9	0.7	1.9	0.9	1.9	1.0	0.0
	(1.4-25.0)	(0.3-1.9)	(0.8-4.1)	(0.5-1.6)	(1.0-3.6)	(0.2-4.0)	(0.0-0.0)
N=20-34 aged, total	**N=35**	**N=202**	**N=95**	**N=240**	**N=116**	**N=24**	**N=67**
Males 20-34 years							
1975-1984	2.8	1.0	0.9	1.3	1.0	1.3	0.9
	(1.5-5.1)	(0.7-1.2)	(0.6-1.3)	(1.0-1.7)	(0.7-1.4)	(0.8-2.0)	(0.4-2.3)
1985-1994	2.1	1.1	0.9	1.4	0.9	0.9	0.8
	(1.0-4.7)	(0.9-1.4)	(0.6-1.5)	(1.1-1.8)	(0.6-1.4)	(0.5-1.5)	(0.4-4.1)
1995-2004	2.3	0.8	1.0	1.0	1.0	1.2	1.1
	(0.7-8.2)	(0.5-1.3)	(0.6-1.9)	(0.7-1.5)	(0.6-1.7)	(0.7-2.3)	(0.8-4.1)
Females 20-34 years							
1975-1984	1.9	1.2	1.2	1.3	1.6	1.4	1.7
	(1.0-3.6)	(0.9-1.6)	(0.8-1.7)	(1.0-1.6)	(1.1-2.2)	(0.9-2.2)	(0.9-3.4)
1985-1994	1.4	1.4	1.2	1.3	1.5	0.9	1.6
	(0.6-3.3)	(1.0-1.8)	(0.8-1.8)	(1.0-1.7)	(1.1-2.2)	(0.6-1.6)	(0.7-3.6)
1995-2004	1.6	1.0	1.4	0.9	1.7	1.4	2.5
	(0.4-5.7)	(0.6-1.6)	(0.8-2.5)	(0.6-1.4)	(1.0-2.8)	(0.7-2.6)	(0.9-6.6)

Table 11. Primary cancer diagnosis associated late psychiatric outcomes in childhood and YA cohorts. Modified from study III, table 4.

Patient group		Organic memory and brain disorder	Alcohol/drug abuse	Schitzophrenia/ psychotic disorders	Mood disorders	Neurotic/ anxiety disorders	Somatization/ eating disorders	Personality disorders
	n	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
ALL								
0-19 years	46	2.3 (0.3-16.6)	0.9 (0.4-2.0)	0.9 (0.4-2.0)	**2.4 (1.4-4.1)**	1.2 (0.7-2.1)	1.8 (0.6-5.7)	0.6 (0.2-1.8)
20-34 years	NA	NA	NA	NA	NA	NA	NA	NA
NHL								
0-19 years	23	6.2 (0.9-44.6)	1.3 (0.5-3.5)	1.9 (0.8-4.6)	2.1 (0.8-5.5)	1.4 (0.6-3.4)	2.2 (0.3-15.5)	1.6 (0.5-4.9)
20-34 years	45	NA	1.4 (0.8-2.4)	1.1 (0.5-2.7)	**1.8 (1.1-3.0)**	1.5 (0.7-3.1)	NA	1.8 (0.7-4.3)
HL								
0-19 years	25	NA	1.0 (0.4-2.3)	1.2 (0.5-2.9)	**2.3 (1.4-4.7)**	1.1 (0.4-2.6)	NA	0.7 (0.2-2.8)
20-34 years	53	1.4 (0.4-5.7)	0.6 (0.3-1.0)	1.1 (0.5-2.7)	1.8 (1.1-3.0)	1.5 (0.7-3.1)	2.7 (1.0-7.3)	0.9 (0.4-2.2)
CNS tumors								
0-19 years	108	**24.0 (13.3-43.2)**	1.2 (0.7-2.1)	**1.7 (1.0-2.8)**	**4.1 (2.9-5.9)**	**1.9 (1.3-2.9)**	2.5 (0.9-6.6)	**2.2 (1.3-3.7)**
20-34 years	84	**9.4 (5.2-17.3)**	1.1 (0.7-1.8)	1.4 (0.8-2.6)	**1.8 (1.2-2.6)**	1.5 (0.8-2.7)	NA	1.0 (0.4-2.5)
Soft tissue								
0-19 years	25	5.3 (0.7-38.6)	1.1 (0.4-3.0)	1.4 (0.5-3.7)	**2.8 (1.3-5.8)**	1.1 (0.4-2.9)	**3.9 (1.0-16.0)**	0.1 (0.2-3.9)
20-34 years	67	0.9 (0.1-6.5)	1.1 (0.7-1.8)	1.4 (0.7-2.6)	**1.8 (1.2-2.7)**	**1.0 (0.5-2.1)**	**3.4 (1.3-9.4)**	1.4 (0.6-3.2)
Kidney								
0-19 years	13	NA	1.8 (0.6-5.7)	NA	**3.4 (1.3-9.0)**	1.5 (0.6-4.1)	NA	1.7 (0.4-6.9)
20-34 years	11	NA	1.7 (0.7-4.7)	**3.1 (1.0-9.8)**	**3.1 (1.0-9.7)**	1.0 (0.1-6.9)	NA	NA
Sympathetic								
0-19 years	7	NA	1.0 (0.1-7.1)	NA	**3.6 (1.1-11.1)**	0.6 (0.1-4.1)	3.1 (0.4-22.1)	1.4 (0.2-9.8)
20-34 years	4	**30.8 (4.3-222.1)**	NA	4.3 (0.6-30.8)	**1.4 (1.1-1.8)**	NA	NA	NA
Thyroid								
0-19 years	16	NA	0.6 (0.2-2.6)	1.4 (0.4-4.2)	1.5 (0.5-4.8)	1.3 (0.4-4.0)	**7.1 (1.8-29.0)**	2.1 (0.7-6.6)
20-34 years	100	**2.5 (1.1-5.7)**	0.7 (0.5-1.1)	1.2 (0.7-2.0)	1.1 (0.8-1.6)	1.3 (0.8-2.0)	2.2 (0.9-5.4)	1.0 (0.5-2.0)
Testis								
0-19 years	8	NA	1.4 (0.3-5.5)	0.9 (0.1-6.3)	**4.0 (1.5-10.7)**	NA	5.6 (0.8-4.1)	NA
20-34 years	73	NA	**1.9 (1.3-2.8)**	1.0 (0.5-2.1)	1.4 (0.9-2.3)	1.5 (0.8-2.7)	1.7 (0.4-7.0)	1.6 (0.8-3.4)

5.3.2 *Analysis of depression medication use by linkage to the Drug Purchase Register (DPR)*

The frequencies of antidepressant (AD) medication purchases were analyzed by the age at cancer diagnosis (0-19 years at diagnosis and 20-34 years at diagnosis) and cumulative incidences are seen in Figure 10.

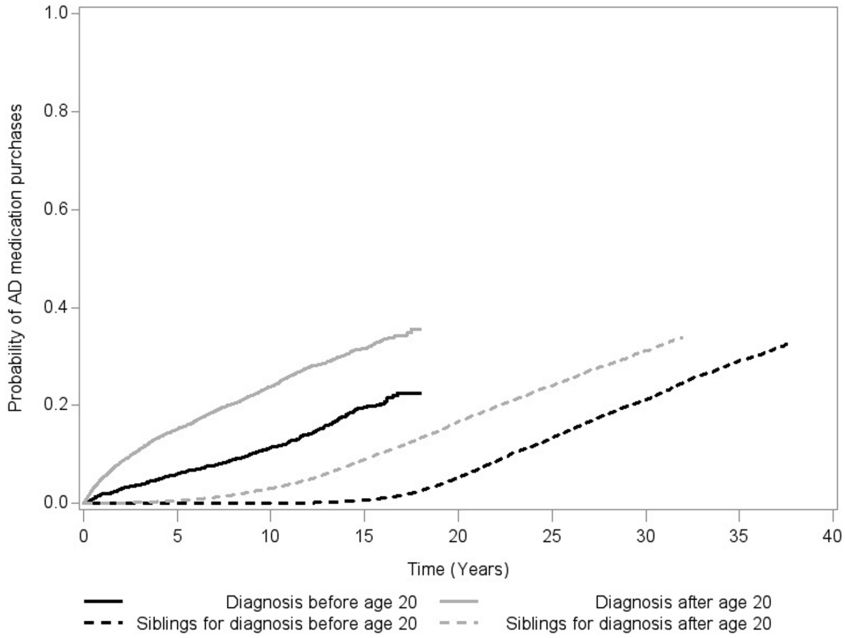


Figure 10. The probability of AD medication purchases of childhood and YA cancer patients and age matched siblings.

Younger [HR 21.0, 95% CI (17.6-25.2)] and older patients [HR 4.9, 95% CI (4.5-5.3)] had an increased risk for being prescribed AD medications compared to their siblings. The data-analysis by gender showed that females had a higher risk for AD medication purchases than male cancer patients or female controls and this finding was consistent in both age groups. In the subgroup analyses, younger sarcoma patients seemed to have the highest risk for AD purchases [HR 33.7, 95 %CI (24.5-46.2)], whereas in the older age group, leukemia patients had the highest risk for AD purchases [HR 9.8, 95% CI (7.6-12.6)] (table 12).

Additionally, an analysis of AD purchases in the era up to the year 1990 and from the year 2000 was performed. In the earlier era, 2.1% of younger cancer patients and 8.6% of older patients had AD purchases, while the corresponding values were 11.4% in the younger and 19.0% in the older patients in the era from 2000 onwards. The HRs (95%CI) for the first time AD purchases compared with siblings, in the

respective eras, were 11.9 (7.7-18.5) and 22.6 (18.6-27.5) in the younger age group, while HRs for older age group were 1.5(1.3-1.8) and 9.3(8.4-10.4).

Table 12. The HRs for AD medication purchases by the age at diagnosis and cancer type. Modified from Study IV, table 2.

Age at diagnosis	Leukemias	Lymphomas	CNS malignancies	Sarcomas	Other malignancies
	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)
0-19 years	15.6 (11.7-20.8)	22.4 (16.9-29.8)	25.7 (20.0-33.4)	33.7 (24.5-46.2)	17.6 (13.4-23.1)
Females	14.9 (10.3-21.6)	24.3 (17.0-34.8)	25.3 (18.1-35.3)	36.9 (24.6-55.4)	17.5 (12.6-24.2)
Males	17.2 (11.4-25.7)	22.2 (14.9-33.0)	28.0 (19.6-40.0)	33.4 (21.4-52.1)	17.5 (11.6-26.5)
	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)	HR (95 % CI)
20-34 years	9.8 (7.6-12.6)	4.3 (3.6-5.0)	7.6 (6.5-9.1)	5.8 (4.8-7.1)	4.4 (4.0-4.8)
Females	8.5 (5.8-12.3)	4.2 (3.4-5.3)	7.4 (6.0-9.3)	5.6 (4.2-7.3)	4.4 (4.0-5.0)
Males	11.9 (8.4-16.7)	4.6 (3.6-5.8)	7.9 (6.1-10.3)	6.4 (4.9-8.6)	3.6 (3.0-4.2)

6 DISCUSSION

6.1 Socio-educational outcomes after young age onset cancer

Late-effect studies have assumed a greater importance in conjunction with the improving 5-year survival of childhood cancer patients. Educational and social outcomes of childhood cancer survivors may affect their employment-, and economical status (Kirchhoff et al. 2011), (Armstrong et al. 2015), (Ehrhardt et al. 2017) and even their marital prospects (Koch et al. 2011), (Font-Gonzalez et al. 2016). Thus, there should be psychosocial supportive measures in-corporated into the follow-up care of childhood and, most probably also AYA cancer survivors.

Neurocognitive deficits may appear several decades after the cancer diagnosis, and the aging process of human brain may accelerate this neurocognitive decline. This project (study I) supports previous findings that BT survivors have the poorest educational outcomes (Reddick et al. 2014), (Lancashire et al. 2010), (Lahteenmaki et al. 2007). The essential treatment procedures, such as cranial irradiation (Packer et al. 1989) and multiagent chemotherapy cannot be avoided. However, modern-day conformal cranial radiation and proton therapy might alleviate these problems by preserving the cognitive performance of those childhood BT survivors that do not need whole brain irradiation (Netson et al. 2013). Modern rehabilitation methods might also be a method of improving the final performance of survivors (Raj et al. 2017).

Previously, it has been shown that female survivors have a higher susceptibility than males of experiencing cognitive and psychosocial late effects (Boman et al. 2009), (Holmqvist et al. 2010). However, Finnish females seem to perform better in the comprehensive school than males, since the education system in Finland seems to favor conscientious girls (Lahteenmaki et al. 2007), and according to current results, female cancer survivors also sit the matriculation examinations of upper secondary school significantly more often than their male cancer patient counterparts. We found that males diagnosed with BT at preschool age achieved poorer results, especially in the first foreign language. In the comprehensive schools, male patients had consistently poorer results in foreign language skills when compared with females, although the gender difference was not so pronounced in other topics. Usually, international reports have suggested that cancer survivors display problems especially with learning mathematics, but this is not evident in Finland (Kaemingk et al. 2004), (Espy et al. 2001).

Treatment related factors and their effect on cognitive and educational outcomes of childhood cancer survivors have been changing during recent decades, partially because cranial irradiation is less often administered as a component of leukemia treatment protocols (Conklin et al. 2012). This is important as there are reports that irradiation affects BT survivors' neurocognitive functioning e.g via diminished white matter volumes and a decline in memory functions, which may continue with time (Reddick et al. 2014), (Armstrong et al. 2013), (Prasad et al. 2015). Potential treatment related brain changes in HL survivors such as leukoencephalopathy have been associated with impaired cognitive functions (Krull et al. 2012). However, for the most part, ST survivors' cognitive attainments do not seem to differ from healthy controls (Lahteenmaki et al. 2008), (Ottaviani et al. 2013), and this was the case in studies I and II. In previous reports, in addition to being due to cranial irradiation impaired memory functioning has been associated with systemic administration of corticosteroids and methotrexate (Boman et al. 2009), (Lancashire et al. 2010), especially in high risk ALL patients (Waber et al. 2012). The results emerging from studies I and II support the previous findings that chemotherapy-only protocols may also be capable of inducing neurocognitive deficits in childhood cancer survivors (Bisen-Hersh, Hineline & Walker 2013), (Shortman et al. 2014), (Kunin-Batson, Kadan-Lottick & Neglia 2014). In the current studies, it was found that irradiation affected survivors' cognitive performance to a lesser extent than has been estimated in previous studies (Harila-Saari et al. 2007), (Lahteenmaki et al. 2008), (Armstrong, Stovall & Robison 2010), (Edelstein et al. 2011). However, the results regarding the effects of irradiation should be viewed with caution because of the low numbers of irradiated patients, especially in study II. Since it was not possible to obtain information on those survivors exempted from the national service in study II, a full picture on the cancer survivors' cognitive and physical performance cannot be attained with this approach. The cognitive results of enlisted survivors lack data on their leadership skills as this is confidential information held by the Finnish Defence Forces.

The results of study I are in keeping with a previous report that concluded that childhood cancer survivors tended to complete only compulsory education (Kuehni et al. 2012). Earlier findings indicate that BT- (Lorenzi et al. 2009), (Boman, Lindblad & Hjern 2010), (Lancashire et al. 2010) and leukemia (Mitby et al. 2003), (Lancashire et al. 2010) survivors were at the highest risk for achieving only a lower educational level, whereas ST survivors have been reported to have equally good educational results as the general population (Koch et al. 2004), (Lahteenmaki et al. 2008). However, it was found in study I that non-graduation from school was common also for leukemia/NHL and ST survivors.

Previous findings on childhood cancer survivors' employment and retirement status gathered from the US and European studies have indicated that these individuals have an increased risk for unemployment compared with either the general population or their siblings (Crom et al. 2007), (Pang et al. 2008), (Holmqvist et al. 2010), (Dieluweit et al. 2011), (Brinkman et al. 2016). In contrast to these previous findings, study I noted that the risk of unemployment was rather low in childhood cancer survivors. This finding may, however, be explained by the higher proportion of premature retirement in Finnish survivors, although retirement has not been estimated in previous studies. Since current treatment procedures contain more brain sparing irradiation approaches, it would be predicted that premature retirement will decline in the future. Poorer physical health, age under seven at diagnosis, and female gender have been recognized as risk factors for unemployment (de Boer, Verbeek & van Dijk 2006), (Kirchhoff et al. 2011). In study I, a gender effect was shown only in BT survivors and even there, males were more likely to be unemployed than females. Retirement was significantly more common in females, but only in survivors of leukemia/NHL. The differences in results between Finland and especially reports from the US are most probably due to the generous Finnish social security system.

It has been reported that adult survivors of childhood cancer appear to manage better in life- if they have a higher educational level- and usually consequently better economic status (Dalton et al. 2008), (Simony et al. 2016). However, in both Swedish and the US studies, childhood cancer survivors have been shown to have a lower income level than the general population (Boman, Lindblad & Hjern 2010), (Hudson et al. 2003). The results obtained in study I are in line with these findings. In order to earn a better income in adulthood, child and young adult cancer survivors should be given optimal educational support as an important component of their psychosocial care.

Changes seem to have occurred in the general atmosphere in Finland, since some of the childhood cancer survivors have been able to enlist for military service as conscripts and coped well with their training; it seems that current acceptance guidelines are quite appropriate.

6.2 Late psychiatric outcomes after young age onset cancer

Cancer in childhood or in young adulthood most probably evokes psychological distress, which may furthermore lead to subsequent adverse late effects such as an increased cardiovascular risk. A lower functional capacity and a poorer quality of life (Wittchen et al. 2011). A lack of supportive follow-up strategies especially in

adolescence regarding school re-entry and the transition to adult care, might worsen the psychological outcomes (Brier, Schwartz & Kazak 2015). Long-term psychological follow-up is warranted since the level of distress may increase long after cancer treatment and symptoms may be persistent (Kunin-Batson et al. 2016), (Maass et al. 2015). In studies III and IV, the hazard ratios for later psychiatric disorders were analyzed by assessing findings also in distinct treatment eras, thereby taking changes in society and cancer treatments into account. Importantly, YA cancer survivors' psychiatric outcomes were also analyzed. Previous data have been very limited for this age group.

Depression has appeared to be the most common psychiatric disorder in the European, US, and the Finnish general population (Wittchen et al. 2011), (Kessler et al. 2005), (Pirkola et al. 2005). Previous findings indicate that especially females in the general population are susceptible to depression and anxiety symptoms in a general population (Kasteenpohja et al. 2015) and there are studies revealing similar outcomes also in cancer survivors (Reimers, Mortensen & Schmiegelow 2007), (Ander et al. 2015), (Deyell et al. 2013), (Inhestern et al. 2017). In questionnaire-based studies conducted in ALL patients, it seems that these individuals do not have a higher level of depression than controls (Gordijn et al. 2013), (Kurtz, Abrams 2011), (Harila et al. 2011). This is somewhat surprising finding, since especially during treatment, corticosteroids are a part of the chemotherapeutic protocol and these agents have been recognized as causing mood disorders (Hochhauser et al. 2005). Furthermore, some other previous studies have reported no higher risk for depression in childhood cancer survivors (Ross et al. 2003), (Schultz et al. 2007). Study III found that in childhood cancer survivors, the risk for mood disorders was elevated in ALL, HL, CNS, soft tissue sarcomas, renal, sympathetic nerve, and testicular tumor survivors. Previous studies, for example the CCCS, have reported that survivors of childhood leukemia (Zebrack et al. 2002), (Myers et al. 2014), HL, NHL (Zebrack et al. 2002), solid tumors (Zebrack et al. 2007) and BTs (Zebrack et al. 2004) are more susceptible to suffering depression and somatic distress (Zebrack et al. 2002) than controls. However, one questionnaire-report based study showed lower psychological distress in survivors of AYA lymphoma and sarcoma (Prasad et al. 2015). There are a few contradictory reports claiming that childhood cancer survivors are not especially susceptible for depression (Pirl et al. 2009), (Harila et al. 2011). In YA cancer survivors, previous surveys have claimed that hormone-related cancer survivors carry an elevated risk for depression (Gorman et al. 2010), (Schultz et al. 2011), (Tai et al. 2012), while study III indicated YA survivors of CNS tumors, soft tissue sarcomas, lymphomas and sympathetic nervous system malignancies to possess the highest risk for experiencing mood disorders.

According to previous studies, organic memory function may be impaired due to cranial radiation therapy (Reimers, Mortensen & Schmiegelow 2007), (Correa et al. 2012). Importantly, the risk for organic memory and brain disorders does not yet seem to have disappeared despite the modifications made to irradiation practices in the cancer treatment protocols.

Earlier studies on anxiety and neurotic disorders after childhood and YA cancer have shown females to have a significantly higher risk for this outcome (Michel et al. 2010), (Zeltzer et al. 2009), (Greer et al. 2011), (Khan et al. 2010a) and it has been suggested that over 30% of adolescent cancer survivors may suffer from this disorder (Ander et al. 2015). The results obtained in study III were consistent with this proposal, especially in survivors of childhood and YA CNS tumors, as well as YA ALL and HL. It was notable that the risk for neurotic and anxiety disorders in female survivors has not declined over the different study periods, indicating a continued need for psychological support system for cancer survivors also later in life.

The increased appearance of psychotic disorders after childhood cancer was reported in one Danish study (Lund et al. 2013), while in study III, childhood BT survivors had an elevated risk compared to siblings, but this difference was not evident in the survivors of YA BTs. Pediatric sarcoma survivors are reported to have higher risk for post-traumatic symptoms appearing even many years post-diagnosis (Wiener et al. 2006), (Rourke et al. 2007). This may be in the background of the increased risk of somatization found in Finnish soft tissue sarcoma survivors (Study III).

Childhood cancer survivors have not been found to display elevated levels of substance use as compared to controls (Rabin, Politi 2010), although contradictory findings have been reported in a Swiss register-based study (Rebholz et al. 2012). The results from study III are consistent with the proposals that there is no excess use. However, a higher risk for alcohol/drug abuse was detected in YA testicular cancer survivors. An alarming finding in females after YA malignancies was that they seemed to have a growing risk for alcohol/drug abuse; this might be attributable to the lack of supportive measures after termination of the actual cancer treatment.

As the frequency of depression in cancer patients may be underestimated when analyzing only hospital data, in Study IV, purchases of antidepressant medication were also analyzed. Previous studies on AD medication purchases have shown that childhood cancer survivors (Deyell et al. 2013), (Lund et al. 2015) and young adult cancer survivors (Deyell et al. 2013) have an excessive risk for AD purchases as compared to controls. The results emerging from study IV are in keeping with this

hypothesis, as the HRs for AD purchases were higher in both age groups. In a Norwegian study, the age at cancer diagnosis did not seem to have any effects on the AD purchases (Johannsdottir et al. 2017). Furthermore, there are three studies reporting the association of AD medication purchases with female gender (Johannsdottir et al. 2017), (Lund et al. 2015), (Brinkman et al. 2016) and the results in study IV are consistent with their findings.

The associations of AD purchases to specific cancer diagnoses have been rarely reported, but there are some indications that childhood and AYA patients of CNS tumor, leukemia (Johannsdottir et al. 2017), testicular malignancies (Johannsdottir et al. 2017), (Khan et al. 2010b) and a group of other malignancies (Johannsdottir et al. 2017) carry an elevated risk for AD purchases. In the subgroup analysis performed in study IV, sarcoma patients in the younger age group and leukemia patients in the YA group were found to have higher HRs for AD purchases. Interestingly, pediatric sarcoma patients have been reported to experience a higher risk for post-traumatic symptoms even many years post-diagnosis (Wiener et al. 2006), (Rourke et al. 2007); in the current study, increased use of AD medication might considered as a reflection of traumatization. YA leukemia patients are often treated with stem cell transplantation, which to some extent might explain the increased use of AD medication. YA cancer patients have been suggested to suffer pre-transplant depression, which reduces the overall survival of these patients due to the higher incidence of post-transplant complications (El-Jawahri et al. 2017). If there is cancer treatment with transplantation, it is plausible that the cancer survivors may suffer not only from toxicities associated with treatment, but also post-transplant late morbidity and mortality, which may reduce their quality of life and induce PTSD and depression (Majhail et al. 2012). With respect to AD medication purchases, there has been an increasing trend during last two decades in both study groups, but there are earlier findings that have revealed similar global trends towards increased numbers of AD prescriptions (Moore et al. 2009). Most importantly, when compared with their siblings, the hazard for first time AD purchases was higher in both age groups even during the recent era. This finding emphasizes why psychological support should be offered to young cancer patients.

6.3 Strengths and limitations of the study

This study has many theoretical and practical strengths. The high-quality national health care and statistical registries confer strengths to this study. National laws ensure the maintenance of these registries, which increases the validity of the register-based data (Leinonen et al. 2017). The Finnish Cancer Registry has been

an essential part of this study, since data on childhood and YA cancer survivors were retrieved from the FCR in studies I-IV. Register-based studies are recognized as having less data bias than large questionnaire-based studies like CCSS (Lund et al. 2011b) and furthermore, registry-based studies are nationwide and population-based with a high number of study subjects.

The fact that cancer survivor data was gathered from several treatment eras can be considered as a strength, as long-term follow-up allows one to make novel observations, for example new findings on late effects. It is beneficial to gather long-term follow-up of childhood cancer survivors, and registry data might make it possible to detect potential late effects, since they may appear even decades after the initial diagnosis. By collating data from different registries, in some study subjects, the follow-up time has extended over thirty years. The follow-up by treatment era makes it feasible to detect possible changes introduced into the cancer treatment protocols (Lund et al. 2015), (Ross et al. 2003).

Educational outcome measures were retrieved from the public registries, and as there is a public educational system in Finland, relatively long-term registry-based information was available both for the survivors and their controls. However, in study I, it must be noted that the numbers of subjects in the different solid tumor diagnosis groups were rather small, which might have meant that some findings did not reach statistical significance.

High exemption rates from compulsory military service have been a rule for childhood cancer survivors in previous years (Lahteenmaki et al. 1999). Since guideline updates have been made, study II gathered important new data on enlisted survivors. These results might have a positive effect on quality of life of survivors. However, it might be difficult to prove this convincingly, because of a lack of quality of life aspect in a register-based setting (Lund et al. 2011b).

Study III produced novel data on psychiatric outcomes of YA cancer survivors. The mixed effects of the results were taken into account e.g. by adjusting the treatment related details and age to maximize the validity of the findings. Furthermore, we assessed psychiatric outcomes by exploiting hospital discharge register-based data, not by patient reported data, which could increase the statistical power of study III's findings. Patients who had previous history of psychiatric diagnoses were excluded in order to determine the effect of cancer on the outcomes more clearly. As psychosocial sequelae are multifactorial and multi–dimensional outcomes, interpretation of results might be complicated because of our inability to adjust for sociodemographic factors. However, the use of a sibling cohort as the control group reduces the effect of genetic predisposition on late adverse mental health late effects. Register-based surveys have produced valuable

data on the etiology of the mental health disparities (Munk-Jorgensen, Ostergaard 2011). The HDR data is gathered by the National Institute of Welfare and Social Services and data gathering and analyses are regulated by the Official Statistics Finland, therefore the HDR data is generally considered to be reliable.

A minor weakness of data of the FCR could be the lack of detailed treatment data (chemotherapy doses, irradiation doses, radiation fields), which restricted the data analyses that could be conducted in studies I-IV, as acknowledged also in previous publications (Lund et al. 2011b).

In study IV, information was available also on the AD prescriptions originated from outside hospitals. Thus, the magnitude of depressive symptoms has been reliably gathered. However, antidepressants may be prescribed also for the treatment of chronic pain, and this possibility could not be differentiated from the purchase registry data. Furthermore, it was not possible to take parental socioeconomic position and psychiatric disease into account. However, there has been an interaction analysis published on data describing the effect of parental socioeconomic position and psychiatric disease on the association between childhood cancer and antidepressant use showing no modifying effect (Lund et al. 2015).

6.4 Follow-up care and future research suggestions

It has been acknowledged that childhood cancer survivors can benefit from follow-up after cancer treatment, and it would be important to find suitable protocols for screening for adverse effects to pinpoint those cancer survivors particularly at risk (Bitsko et al. 2016). Recent outcome findings have shown that the rehabilitation of childhood cancer survivors who have experienced milder adverse effects might be feasible and their functional capacity could be restored (Bisen-Hersh, Hineline & Walker 2013), (Shortman et al. 2014). It would be beneficial to influence the cancer survivors' lifestyle e.g. to encourage them to make healthy lifestyle choices; this might be one way to prevent some of the adverse effects of cancer. However, only some of the tested interventions seem to be effective, but more research will be needed to resolve this issue in the future (Kopp et al.2017).

Guidelines for the follow-up care of childhood cancer survivors have been implemented in many countries (Di Pinto et al. 2012), (Nathan et al. 2007), although Essig et al. showed that follow-up percentages in Europe vary extensively i.e. from 9% to 83%. Furthermore, an optimal follow-up program seemed to be lacking in most European countries (Essig et al. 2012). Currently, existing clinical

practice guidelines, such as SJLIFE and COG long-term follow-up guidelines (LTFU), have been devised to provide information about late effects and treatment-induced health risks (Bhakta et al. 2017), (Bitsko et al. 2016), which could be beneficial in stratifying cancer survivors (Jacobs, Shulman 2017). In an attempt to mitigate the adverse effects of childhood cancer, extensive efforts will be needed to resolve this issue (Bitsko et al. 2016), (Fidler, Hawkins 2017). The availability of LTFU has varied from country to country. The assessment of the cumulative aspect in late morbidities after childhood cancers' might be helpful in planning the follow-up care of survivors with multiple late effects (Bhakta et al. 2017).

Encouraging childhood cancer survivors to make healthy choices later in life is one valuable aspects of follow-up care. Current health promoting interventions have been provided to childhood and AYA cancer survivors with somewhat inconclusive results (Kunin-Batson et al. 2016), (Hollen et al. 2013). However, interventions promoting physical function have hinted at some positive effects in cancer survivors, by assisting these individuals to achieve elevated physical functioning and in that way, to improve their quality of life. However, it seems that the feasibility and repeatability of these interventions have been only inadequately analyzed and thereby a more wide scale implementation of these programs would be beneficial (Baumann, Bloch & Beulertz 2013).

It has been claimed that the adoption of computerized interventions in the care of cancer survivors had produced promising results (Hardy et al. 2013), (Moore et al. 2012). By activating the brain with cognitive programs after a CNS tumor or ALL, survivors have achieved better results in comparison to those prescribed stimulant medications, which had been previously considered as a way to remediate cognitive functioning (Zou et al. 2012), (Hardy, Willard & Bonner 2011), (Patel et al. 2009) or to prevent a cognitive decline (Moore et al. 2012). Positive findings have been made of web-based interventions e.g. in mitigating anxiety symptoms after cancer (Fisher et al. 2015), (Hoybye et al. 2010). The importance of these novel interventions may increase with the number of survivors needing this support, since there are indications that as many as every fifth CNS tumor survivor suffers from anxiety (Wenninger et al. 2013). However, there are challenges to appear be overcome, especially in convincing adolescents to engage in these interventions (Hoybye et al. 2016), and this has reduced the impact of this kind of support. In Finland, the development of "Virtuaalisairaala" with its branches devoted to mental health care (www.mielenterveystalo.fi) may well represent a solution for providing self-help resources to survivors. Recently, in Finland, a three-stepped risk assessment model for the survivors treated for cancer below the age of 25 years was introduced by an expert group of the Ministry of Social Affairs

and Health (http://www.vsshp.fi/fi/toimipaikat/tyks/to8/to8c/step/Sivut/default.aspx).

As the follow-up of childhood cancer survivors ends when the individual reaches adulthood, many survivors will cease to receive any regular follow-up (Freyer 2010). Guidelines are needed for this transitional phase, and efforts in the PANCARE- program in Europe have been taken to devise such guidelines (Brown et al. 2015) Although challenges have been encountered in adult cancer survivors' LTFU care, mainly because of disparities in detecting adverse effect and reporting those effects, up till now, adult follow-up care has been mainly risk-based (COG LTFU guidelines in the USA (www.survivorguidelines.org, version 4.0), rather than being tailored to the survivor's individual needs (Eshelman-Kent et al. 2011).

One of the noteworthy aspects in future follow-up care of childhood cancer survivors might be the exploitation of mobile phone based health care applications, as rapid developments are taking place in these modern techniques (Slater, Fielden & Bradford 2017). Similarly, as in YA survivor care, several mental health self-management solutions (Raj et al. 2017), (Bradford, Chan 2017), and interventions supporting physical functioning via either social media (Mendoza et al. 2017) or a web-based setting are being evaluated (Willems et al. 2017), (Schmidt et al. 2017).

One can suggest several future research topics; for example, findings emerging from this study on childhood cancer survivors showed that they have an increased risk for lower educational level and for early retirement, and thus, efficient rehabilitation and supportive measures should be provided to childhood cancer survivors. Although some kind of structured follow-up care model might be beneficial, it should be appreciated that childhood cancers survivors are not a single group but have individual differences, with the survivors encountering rather different levels of adverse effects and therefore they have variable requirements for support (Bhakta et al. 2017). According to the findings in study III, AYA cancer survivors also need longitudinal support. Research on appropriate supportive methods, follow-up and optimal resource co-ordination are also urgently needed.

7 CONCLUSIONS

1. Childhood BT-, leukemia/NHL and ST survivors had an elevated risk for early retirement and lower economic status compared with population controls, but their risk for unemployment was not elevated. However, early retirement seems to have occurred to a lesser extent in recent years, and this improvement might be attributable to changes in treatment procedures, a reassuring finding. Furthermore, all three survivor groups had a significantly higher risk for not progressing to further education after comprehensive schooling compared to controls. Irradiation was associated with worsened educational and social outcome measures in childhood BT survivors.

2. The guidelines defining who is fit for military service have changed during the last two decades, and a higher proportion of male childhood cancer survivors are nowadays able to perform national service in the military than in previous decades. The physical performance of leukemia/NHL and BT survivors was poorer in 12-minute running test than in controls, whereas survivors' performances in muscular tests were comparable to those of controls, except for standing long jump test. The cognitive performance of survivors was found to be similar to controls, with the exception of BT survivors.

3. Both childhood and YA cancer survivors had an increased risk for psychiatric late-effects compared to their siblings. Furthermore, females and BT survivors were found to have the highest risk for psychiatric sequelae, especially for depression, anxiety and psychotic disorders. Irradiation therapy was not associated with psychiatric outcomes in the survivors.

4. In the study of the usage of anti-depressants by childhood and AYA cancer patients, the cumulative incidence of AD medication purchases was significantly higher in both patient groups than in their siblings. It was found that females carried a greater risk for this outcome. In childhood cancer survivors, sarcoma patients had the highest risk for purchasing AD medications, while in the YA group, leukemia survivors had the highest risk.

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REFERENCES

Allemani, C., Coleman, M.P. & CONCORD Working Group 2015, "Cancer survival: [corrected] the CONCORD-2 study - Authors' reply", *Lancet (London, England),* vol. 386, no. 9992, pp. 429-430.

Ander, M., Gronqvist, H., Cernvall, M., Engvall, G., Hedstrom, M., Ljungman, G., Lyhagen, J., Mattsson, E. & von Essen, L. 2016, "Development of health-related quality of life and symptoms of anxiety and depression among persons diagnosed with cancer during adolescence: a 10-year follow-up study", *Psycho-oncology,* vol. 25, no. 5, pp. 582-589.

Armenian, S.H., Landier, W., Francisco, L., Herrera, C., Mills, G., Siyahian, A., Supab, N., Wilson, K., Wolfson, J.A., Horak, D. & Bhatia, S. 2015, "Long-term pulmonary function in survivors of childhood cancer", *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* vol. 33, no. 14, pp. 1592-1600.

Armstrong, G.T., Chen, Y., Yasui, Y., Leisenring, W., Gibson, T.M., Mertens, A.C., Stovall, M., Oeffinger, K.C., Bhatia, S., Krull, K.R., Nathan, P.C., Neglia, J.P., Green, D.M., Hudson, M.M. & Robison, L.L. 2016, "Reduction in Late Mortality among 5-Year Survivors of Childhood Cancer", *The New England journal of medicine,* vol. 374, no. 9, pp. 833-842.

Armstrong, G.T., Conklin, H.M., Huang, S., Srivastava, D., Sanford, R., Ellison, D.W., Merchant, T.E., Hudson, M.M., Hoehn, M.E., Robison, L.L., Gajjar, A. & Morris, E.B. 2011, "Survival and long-term health and cognitive outcomes after low-grade glioma", *Neuro-oncology,* vol. 13, no. 2, pp. 223-234.

Armstrong, G.T., Joshi, V.M., Ness, K.K., Marwick, T.H., Zhang, N., Srivastava, D., Griffin, B.P., Grimm, R.A., Thomas, J., Phelan, D., Collier, P., Krull, K.R., Mulrooney, D.A., Green, D.M., Hudson, M.M., Robison, L.L. & Plana, J.C. 2015, "Comprehensive Echocardiographic Detection of Treatment-Related Cardiac Dysfunction in Adult Survivors of Childhood Cancer: Results From the St. Jude Lifetime Cohort Study", *Journal of the American College of Cardiology,* vol. 65, no. 23, pp. 2511-2522.

Armstrong, G.T., Liu, Q., Yasui, Y., Huang, S., Ness, K.K., Leisenring, W., Hudson, M.M., Donaldson, S.S., King, A.A., Stovall, M., Krull, K.R., Robison, L.L. & Packer, R.J. 2009a, "Long-term outcomes among adult survivors of childhood central nervous system malignancies in the Childhood Cancer Survivor Study", *Journal of the National Cancer Institute,* vol. 101, no. 13, pp. 946-958.

Armstrong, G.T., Liu, Q., Yasui, Y., Neglia, J.P., Leisenring, W., Robison, L.L. & Mertens, A.C. 2009b, "Late mortality among 5-year survivors of childhood cancer: a summary from the Childhood Cancer Survivor Study", *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* vol. 27, no. 14, pp. 2328-2338.

Armstrong, G.T., Reddick, W.E., Petersen, R.C., Santucci, A., Zhang, N., Srivastava, D., Ogg, R.J., Hillenbrand, C.M., Sabin, N., Krasin, M.J., Kun, L., Pui, C.H., Hudson, M.M., Robison, L.L. & Krull, K.R. 2013, "Evaluation of memory impairment in aging adult survivors of childhood acute lymphoblastic leukemia treated with cranial radiotherapy", *Journal of the National Cancer Institute,* vol. 105, no. 12, pp. 899-907.

Armstrong, G.T., Stovall, M. & Robison, L.L. 2010, "Long-term effects of radiation exposure among adult survivors of childhood cancer: results from the childhood cancer survivor study", *Radiation research,* vol. 174, no. 6, pp. 840-850.

Asdahl, P.H., Winther, J.F., Bonnesen, T.G., De Fine Licht, S., Gudmundsdottir, T., Anderson, H., Madanat-Harjuoja, L., Tryggvadottir, L., Smastuen, M.C., Holmqvist, A.S., Hasle, H., Olsen, J.H. & ALiCCS Study Group 2015, "The Adult Life After Childhood Cancer in Scandinavia (ALiCCS) Study: Design and Characteristics", *Pediatric blood & cancer,* vol. 62, no. 12, pp. 2204-2210.

Askins, M.A. & Moore, B.D.,3rd 2008, "Preventing neurocognitive late effects in childhood cancer survivors", *Journal of child neurology,* vol. 23, no. 10, pp. 1160-1171.

Bardwell, W.A., Profant, J., Casden, D.R., Dimsdale, J.E., Ancoli-Israel, S., Natarajan, L., Rock, C.L., Pierce, J.P. & Women's Healthy Eating & Living (WHEL) Study Group 2008, "The relative importance of specific risk factors for insomnia in women treated for early-stage breast cancer", *Psycho-oncology,* vol. 17, no. 1, pp. 9-18.

Battaglini, C.L., Mills, R.C., Phillips, B.L., Lee, J.T., Story, C.E., Nascimento, M.G. & Hackney, A.C. 2014, "Twenty-five years of research on the effects of exercise training in breast cancer survivors: A systematic review of the literature", *World journal of clinical oncology,* vol. 5, no. 2, pp. 177-190.

Baumann, F.T., Bloch, W. & Beulertz, J. 2013, "Clinical exercise interventions in pediatric oncology: a systematic review", *Pediatric research,* vol. 74, no. 4, pp. 366-374.

Berry, D.L., Hong, F., Halpenny, B., Partridge, A.H., Fann, J.R., Wolpin, S., Lober, W.B., Bush, N.E., Parvathaneni, U., Back, A.L., Amtmann, D. & Ford, R. 2014, "Electronic self-report assessment for cancer and self-care support: results of a multicenter randomized trial", *Journal of clinical oncology : official journal of the American Society of Clinical Oncology,* vol. 32, no. 3, pp. 199-205.

Bhakta, N., Liu, Q., Ness, K.K., Baassiri, M., Eissa, H., Yeo, F., Chemaitilly, W., Ehrhardt, M.J., Bass, J., Bishop, M.W., Shelton, K., Lu, L., Huang, S., Li, Z., Caron, E., Lanctot, J., Howell, C., Folse, T., Joshi, V., Green, D.M., Mulrooney, D.A., Armstrong, G.T., Krull, K.R., Brinkman, T.M., Khan, R.B., Srivastava, D.K., Hudson, M.M., Yasui, Y. & Robison, L.L. 2017, "The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE)", *Lancet (London, England),* vol. 390, no. 10112, pp. 2569-2582.

Bhatia, S. 2011, "Role of genetic susceptibility in development of treatment-related adverse outcomes in cancer survivors", Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, vol. 20, no. 10, pp. 2048-2067.

Bisen-Hersh, E.B., Hineline, P.N. & Walker, E.A. 2013, "Effects of early chemotherapeutic treatment on learning in adolescent mice: implications for cognitive impairment and remediation in childhood cancer survivors", Clinical cancer research : an official journal of the American Association for Cancer Research, vol. 19, no. 11, pp. 3008-3018.

Bitsko, M.J., Cohen, D., Dillon, R., Harvey, J., Krull, K. & Klosky, J.L. 2016, "Psychosocial Late Effects in Pediatric Cancer Survivors: A Report From the Children's Oncology Group", Pediatric blood & cancer, vol. 63, no. 2, pp. 337-343.

Blaauwbroek, R., Groenier, K.H., Kamps, W.A., Meyboom-de Jong, B. & Postma, A. 2007, "Late effects in adult survivors of childhood cancer: the need for life-long follow-up", Annals of oncology : official journal of the European Society for Medical Oncology, vol. 18, no. 11, pp. 1898-1902.

Boman, K.K., Hoven, E., Anclair, M., Lannering, B. & Gustafsson, G. 2009, "Health and persistent functional late effects in adult survivors of childhood CNS tumours: a population-based cohort study", European journal of cancer (Oxford, England : 1990), vol. 45, no. 14, pp. 2552-2561.

Boman, K.K., Lindblad, F. & Hjern, A. 2010, "Long-term outcomes of childhood cancer survivors in Sweden: a population-based study of education, employment, and income", Cancer, vol. 116, no. 5, pp. 1385-1391.

Bonneau, J., Lebreton, J., Taque, S., Chappe, C., Bayart, S., Edan, C. & Gandemer, V. 2011, "School performance of childhood cancer survivors: mind the teenagers!", The Journal of pediatrics, vol. 158, no. 1, pp. 135-141.

Bradford, N.K. & Chan, R.J. 2017, "Health promotion and psychological interventions for adolescent and young adult cancer survivors: A systematic literature review", Cancer treatment reviews, vol. 55, pp. 57-70.

Brier, M.J., Schwartz, L.A. & Kazak, A.E. 2015, "Psychosocial, health-promotion, and neurocognitive interventions for survivors of childhood cancer: a systematic review", Health psychology : official journal of the Division of Health Psychology, American Psychological Association, vol. 34, no. 2, pp. 130-148.

Brinkman, T.M., Krasin, M.J., Liu, W., Armstrong, G.T., Ojha, R.P., Sadighi, Z.S., Gupta, P., Kimberg, C., Srivastava, D., Merchant, T.E., Gajjar, A., Robison, L.L., Hudson, M.M. & Krull, K.R. 2016, "Long-Term Neurocognitive Functioning and Social Attainment in Adult Survivors of Pediatric CNS Tumors: Results From the St Jude Lifetime Cohort Study", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 34, no. 12, pp. 1358-1367.

Brinkman, T.M., Li, C., Vannatta, K., Marchak, J.G., Lai, J.S., Prasad, P.K., Kimberg, C., Vuotto, S., Di, C., Srivastava, D., Robison, L.L., Armstrong, G.T. & Krull, K.R. 2016, "Behavioral, Social, and Emotional Symptom Comorbidities and Profiles in Adolescent Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 34, no. 28, pp. 3417-3425.

Brinkman, T.M., Reddick, W.E., Luxton, J., Glass, J.O., Sabin, N.D., Srivastava, D.K., Robison, L.L., Hudson, M.M. & Krull, K.R. 2012, "Cerebral white matter integrity and executive function in adult survivors of childhood medulloblastoma", Neuro-oncology, vol. 14 Suppl 4, pp. iv25-36.

Brown, M.C., Levitt, G.A., Frey, E., Bardi, E., Haupt, R., Hjorth, L., Kremer, L., Kuehni, C.E., Lettner, C., Mulder, R.L., Michel, G., Skinner, R. & PanCareSurFup Consortium 2015, "The views of European clinicians on guidelines for long-term follow-up of childhood cancer survivors", Pediatric blood & cancer, vol. 62, no. 2, pp. 322-328.

Campbell, L.K., Scaduto, M., Sharp, W., Dufton, L., Van Slyke, D., Whitlock, J.A. & Compas, B. 2007, "A meta-analysis of the neurocognitive sequelae of treatment for childhood acute lymphocytic leukemia", Pediatric blood & cancer, vol. 49, no. 1, pp. 65-73.

Casey, B.J., Getz, S. & Galvan, A. 2008, "The adolescent brain", Developmental review: DR, vol. 28, no. 1, pp. 62-77.

Conklin, H.M., Krull, K.R., Reddick, W.E., Pei, D., Cheng, C. & Pui, C.H. 2012, "Cognitive outcomes following contemporary treatment without cranial irradiation for childhood acute lymphoblastic leukemia", Journal of the National Cancer Institute, vol. 104, no. 18, pp. 1386-1395.

Cooper, K.H. 1968, "A means of assessing maximal oxygen intake. Correlation between field and treadmill testing", JAMA : the journal of the American Medical Association, vol. 203, no. 3, pp. 201-204.

Correa, D.D., Shi, W., Abrey, L.E., Deangelis, L.M., Omuro, A.M., Deutsch, M.B. & Thaler, H.T. 2012, "Cognitive functions in primary CNS lymphoma after single or combined modality regimens", Neuro-oncology, vol. 14, no. 1, pp. 101-108.

Crom, D.B., Lensing, S.Y., Rai, S.N., Snider, M.A., Cash, D.K. & Hudson, M.M. 2007, "Marriage, employment, and health insurance in adult survivors of childhood cancer", Journal of cancer survivorship: research and practice, vol. 1, no. 3, pp. 237-245.

Daams, M., Schuitema, I., van Dijk, B.W., van Dulmen-den Broeder, E., Veerman, A.J., van den Bos, C. & de Sonneville, L.M. 2012, "Long-term effects of cranial irradiation and intrathecal chemotherapy in treatment of childhood leukemia: a MEG study of power spectrum and correlated cognitive dysfunction", BMC neurology, vol. 12, pp. 84-2377-12-84.

D'Agostino, N.M. & Edelstein, K. 2013, "Psychosocial challenges and resource needs of young adult cancer survivors: implications for program development", Journal of Psychosocial Oncology, vol. 31, no. 6, pp. 585-600.

D'Agostino, N.M., Penney, A. & Zebrack, B. 2011, "Providing developmentally appropriate psychosocial care to adolescent and young adult cancer survivors", Cancer, vol. 117, no. 10 Suppl, pp. 2329-2334.

Dalton, S.O., Laursen, T.M., Ross, L., Mortensen, P.B. & Johansen, C. 2009, "Risk for hospitalization with depression after a cancer diagnosis: a nationwide, population-based study of cancer patients in Denmark from 1973 to 2003", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 27, no. 9, pp. 1440-1445.

Dalton, S.O., Steding-Jessen, M., Engholm, G., Schuz, J. & Olsen, J.H. 2008, "Social inequality and incidence of and survival from lung cancer in a population-based study in Denmark, 1994-2003", European journal of cancer (Oxford, England : 1990), vol. 44, no. 14, pp. 1989-1995.

Daniel, L., Kazak, A.E., Li, Y., Hobbie, W., Ginsberg, J., Butler, E. & Schwartz, L. 2015, "Relationship between sleep problems and psychological outcomes in adolescent and young adult cancer survivors and controls", Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, .

Daszkiewicz, P., Maryniak, A., Roszkowski, M. & Barszcz, S. 2009, "Long-term functional outcome of surgical treatment of juvenile pilocytic astrocytoma of the cerebellum in children", Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery, vol. 25, no. 7, pp. 855-860.

Davies, N.J. & Batehup, L. 2011, "Towards a personalised approach to aftercare: a review of cancer follow-up in the UK", Journal of cancer survivorship : research and practice, vol. 5, no. 2, pp. 142-151.

De Angelis, R., Sant, M., Coleman, M.P., Francisci, S., Baili, P., Pierannunzio, D., Trama, A., Visser, O., Brenner, H., Ardanaz, E., Bielska-Lasota, M., Engholm, G., Nennecke, A., Siesling, S., Berrino, F., Capocaccia, R. & EUROCARE-5 Working Group 2014, "Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study", The Lancet.Oncology, vol. 15, no. 1, pp. 23-34.

de Boer, A.G., Verbeek, J.H. & van Dijk, F.J. 2006, "Adult survivors of childhood cancer and unemployment: A metaanalysis", Cancer, vol. 107, no. 1, pp. 1-11.

de Fine Licht, S., Rugbjerg, K., Gudmundsdottir, T., Bonnesen, T.G., Asdahl, P.H., Holmqvist, A.S., Madanat-Harjuoja, L., Tryggvadottir, L., Wesenberg, F., Hasle, H., Winther, J.F., Olsen, J.H. & ALiCCS study group 2017, "Long-term inpatient disease burden in the Adult Life after Childhood Cancer in Scandinavia (ALiCCS) study: A cohort study of 21,297 childhood cancer survivors", PLoS medicine, vol. 14, no. 5, pp. e1002296.

Devine, K.A., Mertens, A.C., Whitton, J.A., Wilson, C.L., Ness, K.K., Gilleland Marchak, J., Leisenring, W., Oeffinger, K.C., Robison, L.L., Armstrong, G.T. & Krull, K.R. 2017, "Factors associated with physical activity among adolescent and young adult survivors of early childhood cancer: A report from the childhood cancer survivor study (CCSS)", Psycho-oncology, .

de Vries, Y.A., de Jonge, P., Kalverdijk, L., Bos, J.H., Schuiling-Veninga, C.C. & Hak, E. 2016, "Poor guideline adherence in the initiation of antidepressant treatment in children and adolescents in the Netherlands: choice of antidepressant and dose", European child & adolescent psychiatry, vol. 25, no. 11, pp. 1161-1170.

Deyell, R.J., Lorenzi, M., Ma, S., Rassekh, S.R., Collet, J.P., Spinelli, J.J. & McBride, M.L. 2013, "Antidepressant use among survivors of childhood, adolescent and young adult cancer: a report of the Childhood, Adolescent and Young Adult Cancer Survivor (CAYACS) Research Program", Pediatric blood & cancer, vol. 60, no. 5, pp. 816-822.

Di Pinto, M., Conklin, H.M., Li, C. & Merchant, T.E. 2012, "Learning and memory following conformal radiation therapy for pediatric craniopharyngioma and low-grade glioma", International journal of radiation oncology, biology, physics, vol. 84, no. 3, pp. e363-9.

Dieluweit, U., Debatin, K.M., Grabow, D., Kaatsch, P., Peter, R., Seitz, D.C. & Goldbeck, L. 2011, "Educational and vocational achievement among long-term survivors of adolescent cancer in Germany", Pediatric blood & cancer, vol. 56, no. 3, pp. 432-438.

Dieluweit, U., Seitz, D.C., Besier, T., Debatin, K.M., Grabow, D., Kaatsch, P. & Goldbeck, L. 2011, "Utilization of psychosocial care and oncological follow-up assessments among German long-term survivors of cancer with onset during adolescence", Klinische Padiatrie, vol. 223, no. 3, pp. 152-158.

Drozdowicz, L.B. & Bostwick, J.M. 2014, "Psychiatric adverse effects of pediatric corticosteroid use", Mayo Clinic proceedings, vol. 89, no. 6, pp. 817-834.

Fujisawa, D., Inoguchi, H., Shimoda, H., Yoshiuchi, K., Inoue, S., Ogawa, A., Okuyama, T., Akechi, T., Mimura, M., Shimizu, K. & Uchitomi, Y. 2015, "Impact of depression on health utility value in cancer patients", Psycho-oncology, .

Edelstein, K., Spiegler, B.J., Fung, S., Panzarella, T., Mabbott, D.J., Jewitt, N., D'Agostino, N.M., Mason, W.P., Bouffet, E., Tabori, U., Laperriere, N. & Hodgson, D.C. 2011, "Early aging in adult survivors of childhood medulloblastoma: long-term neurocognitive, functional, and physical outcomes", Neuro-oncology, vol. 13, no. 5, pp. 536-545.

Ehrhardt, M.J., Mulrooney, D.A., Li, C., Baassiri, M.J., Bjornard, K., Sandlund, J.T., Brinkman, T.M., Huang, I.C., Srivastava, D.K., Ness, K.K., Robison, L.L., Hudson, M.M. & Krull, K.R. 2017, "Neurocognitive, psychosocial, and quality-of-life outcomes in adult survivors of childhood non-Hodgkin lymphoma", Cancer, .

ElAlfy, M., Ragab, I., Azab, I., Amin, S. & Abdel-Maguid, M. 2014, "Neurocognitive outcome and white matter anisotropy in childhood acute lymphoblastic leukemia survivors treated with different protocols", Pediatric hematology and oncology, vol. 31, no. 2, pp. 194-204.

El-Jawahri, A., Chen, Y.B., Brazauskas, R., He, N., Lee, S.J., Knight, J.M., Majhail, N., Buchbinder, D., Schears, R.M., Wirk, B.M., Wood, W.A., Ahmed, I., Aljurf, M., Szer, J., Beattie, S.M., Battiwalla, M.,

Dandoy, C., Diaz, M.A., D'Souza, A., Freytes, C.O., Gajewski, J., Gerqis, U., Hashmi, S.K., Jakubowski, A., Kamble, R.T:, Kindwall-Keller, T., Lazarus, H.M., Malone, A.K., Marks, D.I, Meehan, K., Savani, B.N., Olsson, R.F., Rizzieri, D., Steinberg, A., Speckhart, D., Szwajcer, D, Schoemans, H., Seo, S., Ustun, C., Atsuta, Y., Dalal, J., Sales-Bonfim, C., Khera, N., Hahn, T., Saber, W., 2017, "Impact of pre-transplant depression on outcomes of allogenic and autologous hematopoietic stem cell transplantation", Cancer, vol. 123, no. 10, pp. 1828-1838.

Ellenberg, L., Liu, Q., Gioia, G., Yasui, Y., Packer, R.J., Mertens, A., Donaldson, S.S., Stovall, M., Kadan-Lottick, N., Armstrong, G., Robison, L.L. & Zeltzer, L.K. 2009, "Neurocognitive status in long-term survivors of childhood CNS malignancies: a report from the Childhood Cancer Survivor Study", Neuropsychology, vol. 23, no. 6, pp. 705-717.

Eshelman-Kent, D., Kinahan, K.E., Hobbie, W., Landier, W., Teal, S., Friedman, D., Nagarajan, R. & Freyer, D.R. 2011, "Cancer survivorship practices, services, and delivery: a report from the Children's Oncology Group (COG) nursing discipline, adolescent/young adult, and late effects committees", Journal of cancer survivorship : research and practice, vol. 5, no. 4, pp. 345-357.

Espy, K.A., Moore, I.M., Kaufmann, P.M., Kramer, J.H., Matthay, K. & Hutter, J.J. 2001, "Chemotherapeutic CNS prophylaxis and neuropsychologic change in children with acute lymphoblastic leukemia: a prospective study", Journal of pediatric psychology, vol. 26, no. 1, pp. 1-9.

Essig, S., Li, Q., Chen, Y., Hitzler, J., Leisenring, W., Greenberg, M., Sklar, C., Hudson, M.M., Armstrong, G.T., Krull, K.R., Neglia, J.P., Oeffinger, K.C., Robison, L.L., Kuehni, C.E., Yasui, Y. & Nathan, P.C. 2014, "Risk of late effects of treatment in children newly diagnosed with standard-risk acute lymphoblastic leukaemia: a report from the Childhood Cancer Survivor Study cohort", The Lancet.Oncology, vol. 15, no. 8, pp. 841-851.

Essig, S., Skinner, R., von der Weid, N.X., Kuehni, C.E. & Michel, G. 2012, "Follow-up programs for childhood cancer survivors in Europe: a questionnaire survey", PloS one, vol. 7, no. 12, pp. e53201.

Fernandez-Pineda, I., Hudson, M.M., Pappo, A.S., Bishop, M.W., Klosky, J.L., Brinkman, T.M., Srivastava, D.K., Neel, M.D., Rao, B.N., Davidoff, A.M., Krull, K.R., Mulrooney, D.A., Robison, L.L., Ness, K.K. 2017, " Long-term functional outcomes and quality of life in adult survivors of childhood extremity sarcomas: a report from St. Jude Lifetime Cohort Study", Journal of Cancer Survivorship, vol. 11, no. 1, pp. 1-12.

Fidler, M.M. & Hawkins, M.M. 2017, "Childhood cancer: the long-term costs of cure", Lancet (London, England), vol. 390, no. 10112, pp. 2530-2531.

Firoozi, M., Besharat, M.A. & Rahimian Boogar, E. 2013, "Emotional regulation and adjustment to childhood cancer: role of the biological, psychological and social regulators on pediatric oncology adjustment", Iranian journal of cancer prevention, vol. 6, no. 2, pp. 65-72.

Fisher, P.L., McNicol, K., Young, B., Smith, E. & Salmon, P. 2015, "Alleviating Emotional Distress in Adolescent and Young Adult Cancer Survivors: An Open Trial of Metacognitive Therapy", Journal of adolescent and young adult oncology, vol. 4, no. 2, pp. 64-69.

Font-Gonzalez, A., Feijen, E.L., Sieswerda, E., van Dulmen-den Broeder, E., Grootenhuis, M., Maurice-Stam, H., Caron, H., Essink-Bot, M.L., van der Pal, H., Geskus, R. & Kremer, L. 2016, "Social outcomes in adult survivors of childhood cancer compared to the general population: linkage of a cohort with population registers", Psycho-oncology, vol. 25, no. 8, pp. 933-941.

Ford, J.S., Chou, J.F. & Sklar, C.A. 2013, "Attendance at a survivorship clinic: impact on knowledge and psychosocial adjustment", Journal of cancer survivorship: research and practice, vol. 7, no. 4, pp. 535-543.

Freyer, D.R. 2010, "Transition of care for young adult survivors of childhood and adolescent cancer: rationale and approaches", Journal of clinical oncology: official journal of the American Society of Clinical Oncology, vol. 28, no. 32, pp. 4810-4818.

Fujisawa, D., Inoguchi, H., Shimoda, H., Yoshiuchi, K., Inoue, S., Ogawa, A., Okuyama, T., Akechi, T., Mimura, M., Shimizu, K., Uchitomi, Y., 2016, "Impact of depression on health utility value in cancer patients", Psycho-oncology, vol. 25, no. 5, pp.491-495.

Garwicz, S., Anderson, H., Olsen, J.H., Winther, J.F., Sankila, R., Langmark, F., Tryggvadottir, L., Moller, T.R., Association of the Nordic Cancer Registries & Nordic Society for Pediatric Hematology Oncology 2012, "Late and very late mortality in 5-year survivors of childhood cancer: changing pattern over four decades--experience from the Nordic countries", International journal of cancer, vol. 131, no. 7, pp. 1659-1666.

Gatta, G., Botta, L., Rossi, S., Aareleid, T., Bielska-Lasota, M., Clavel, J., Dimitrova, N., Jakab, Z., Kaatsch, P., Lacour, B., Mallone, S., Marcos-Gragera, R., Minicozzi, P., Sanchez-Perez, M.J., Sant, M., Santaquilani, M., Stiller, C., Tavilla, A., Trama, A., Visser, O., Peris-Bonet, R. & EUROCARE Working Group 2014, "Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5--a population-based study", The Lancet.Oncology, vol. 15, no. 1, pp. 35-47.

Geenen, M.M., Cardous-Ubbink, M.C., Kremer, L.C., van den Bos, C., van der Pal, H.J., Heinen, R.C., Jaspers, M.W., Koning, C.C., Oldenburger, F., Langeveld, N.E., Hart, A.A., Bakker, P.J., Caron, H.N. & van Leeuwen, F.E. 2007, "Medical assessment of adverse health outcomes in long-term survivors of childhood cancer", JAMA : the journal of the American Medical Association, vol. 297, no. 24, pp. 2705-2715.

Goldsby, R.E., Liu, Q., Nathan, P.C., Bowers, D.C., Yeaton-Massey, A., Raber, S.H., Hill, D., Armstrong, G.T., Yasui, Y., Zeltzer, L., Robison, L.L. & Packer, R.J. 2010, "Late-occurring neurologic sequelae in adult survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer

Survivor Study", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 28, no. 2, pp. 324-331.

Gordijn, M.S., van Litsenburg, R.R., Gemke, R.J., Huisman, J., Bierings, M.B., Hoogerbrugge, P.M. & Kaspers, G.J. 2013, "Sleep, fatigue, depression, and quality of life in survivors of childhood acute lymphoblastic leukemia", Pediatric blood & cancer, vol. 60, no. 3, pp. 479-485.

Gorman, J.R., Malcarne, V.L., Roesch, S.C., Madlensky, L. & Pierce, J.P. 2010, "Depressive symptoms among young breast cancer survivors: the importance of reproductive concerns", Breast cancer research and treatment, vol. 123, no. 2, pp. 477-485.

Green, D.M., Zhu, L., Wang, M., Ness, K.K., Krasin, M.J., Bhakta, N.H., McCarville, M.B., Srinivasan, S., Stokes, D.C., Srivastava, D., Ojha, R., Shelton, K., Pui, C.H., Armstrong, G.T., Mulrooney, D.A., Metzger, M., Spunt, S.L., Navid, F., Davidoff, A.M., Rao, B.N., Robison, L.L. & Hudson, M.M. 2016, "Pulmonary Function after Treatment for Childhood Cancer. A Report from the St. Jude Lifetime Cohort Study (SJLIFE)", Annals of the American Thoracic Society, vol. 13, no. 9, pp. 1575-1585.

Greenfield, D.M., Walters, S.J., Coleman, R.E., Hancock, B.W., Snowden, J.A., Shalet, S.M., DeRogatis, L.R. & Ross, R.J. 2010, "Quality of life, self-esteem, fatigue, and sexual function in young men after cancer: a controlled cross-sectional study", Cancer, vol. 116, no. 6, pp. 1592-1601.

Greer, J.A., Solis, J.M., Temel, J.S., Lennes, I.T., Prigerson, H.G., Maciejewski, P.K. & Pirl, W.F. 2011, "Anxiety disorders in long-term survivors of adult cancers", Psychosomatics, vol. 52, no. 5, pp. 417-423.

Gunnes, M.W., Lie, R.T., Bjorge, T., Ghaderi, S., Syse, A., Ruud, E., Wesenberg, F. & Moster, D. 2017, "Suicide and violent deaths in survivors of cancer in childhood, adolescence and young adulthood-A national cohort study", International journal of cancer, vol. 140, no. 3, pp. 575-580.

Gurney, J.G., Krull, K.R., Kadan-Lottick, N., Nicholson, H.S., Nathan, P.C., Zebrack, B., Tersak, J.M. & Ness, K.K. 2009, "Social outcomes in the Childhood Cancer Survivor Study cohort", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 27, no. 14, pp. 2390-2395.

Gyllenberg, D., Sourander, A., Niemela, S., Helenius, H., Sillanmaki, L., Ristkari, T., Piha, J., Kumpulainen, K., Tamminen, T., Moilanen, I. & Almqvist, F. 2011, "Childhood predictors of use and costs of antidepressant medication by age 24 years: findings from the Finnish Nationwide 1981 Birth Cohort Study", Journal of the American Academy of Child and Adolescent Psychiatry, vol. 50, no. 4, pp. 406-15, 415.e1

Hardy, K.K., Willard, V.W., Allen, T.M. & Bonner, M.J. 2013, "Working memory training in survivors of pediatric cancer: a randomized pilot study", Psycho-oncology, vol. 22, no. 8, pp. 1856-1865.

Hardy, K.K., Willard, V.W. & Bonner, M.J. 2011, "Computerized cognitive training in survivors of childhood cancer: a pilot study", Journal of pediatric oncology nursing : official journal of the Association of Pediatric Oncology Nurses, vol. 28, no. 1, pp. 27-33.

Harila, M.J., Niinivirta, T.I., Winqvist, S. & Harila-Saari, A.H. 2011, "Low depressive symptom and mental distress scores in adult long-term survivors of childhood acute lymphoblastic leukemia", Journal of pediatric hematology/oncology, vol. 33, no. 3, pp. 194-198.

Harila, M.J., Winqvist, S., Lanning, M., Bloigu, R. & Harila-Saari, A.H. 2009, "Progressive neurocognitive impairment in young adult survivors of childhood acute lymphoblastic leukemia", Pediatric blood & cancer, vol. 53, no. 2, pp. 156-161.

Harila-Saari, A.H., Lahteenmaki, P.M., Pukkala, E., Kyyronen, P., Lanning, M. & Sankila, R. 2007, "Scholastic achievements of childhood leukemia patients: a nationwide, register-based study", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 25, no. 23, pp. 3518-3524.

Hartman, A., van den Bos, C., Stijnen, T. & Pieters, R. 2006, "Decrease in motor performance in children with cancer is independent of the cumulative dose of vincristine", Cancer, vol. 106, no. 6, pp. 1395-1401.

Hawkins, M.M., Lancashire, E.R., Winter, D.L., Frobisher, C., Reulen, R.C., Taylor, A.J., Stevens, M.C., Jenney, M., 2008, “The British Childhood Cancer Survivor Study: Objectives, methods, population structure, response rates, and initial descriptive information”, *Pediatr Blood Cancer*, vol. 50, no. 5, pp.1018-1025.

Hawkins, M.M. & Robison, L.L. 2006, "Importance of clinical and epidemiological research in defining the long-term clinical care of pediatric cancer survivors", Pediatric blood & cancer, vol. 46, no. 2, pp. 174-178.

Hawkins, N.A., Soman, A., Buchanan-Lunsford, N., Leadbetter, S., Rodrigues, J.L., 2017, “Use of Medications for Treating Anxiety and Depression in Cancer Survivors in the United States”, J Clin Oncol, vol. 35, no. 1, pp. 78-85.

Hjorth, L., Haupt, R., Skinner, R., Grabow, D., Byrne, J., Karner, S., Levitt, G., Michel, G., van der Pal, H., Bardi, E., Beck, J.D., de Vathaire, F., Essig, S., Frey, E., Garwicz, S., Hawkins, M., Jakab, Z., Jankovic, M., Kazanowska, B., Kepak, T., Kremer, L., Lackner, H., Sugden, E., Terenziani, M., Zaletel, L.Z., Kaatsch, P. & PanCare Network 2015, "Survivorship after childhood cancer: PanCare: a European Network to promote optimal long-term care", European journal of cancer (Oxford, England : 1990), vol. 51, no. 10, pp. 1203-1211.

Hochhauser, C.J., Lewis, M., Kamen, B.A. & Cole, P.D. 2005, "Steroid-induced alterations of mood and behavior in children during treatment for acute lymphoblastic leukemia", Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, vol. 13, no. 12, pp. 967-974.

Hoffman, M.C., Mulrooney, D.A., Steinberger, J., Lee, J., Baker, K.S. & Ness, K.K. 2013, "Deficits in physical function among young childhood cancer survivors", Journal of clinical oncology : official

journal of the American Society of Clinical Oncology, vol. 31, no. 22, pp. 2799-2805.

Hollen, P.J., Tyc, V.L., Donnangelo, S.F., Shannon, S.V., O'Laughlen, M.C., Hinton, I., Smolkin, M.E. & Petroni, G.R. 2013, "A substance use decision aid for medically at-risk adolescents: results of a randomized controlled trial for cancer-surviving adolescents", Cancer nursing, vol. 36, no. 5, pp. 355-367.

Holmqvist, A.S., Wiebe, T., Hjorth, L., Lindgren, A., Ora, I. & Moell, C. 2010, "Young age at diagnosis is a risk factor for negative late socio-economic effects after acute lymphoblastic leukemia in childhood", Pediatric blood & cancer, vol. 55, no. 4, pp. 698-707.

Holmqvist, A.S., Olsen, J.H., Andersen, K.K., de Fine-Licht, S., Hjorth, L., Garwicz, S., Moell, C., Anderson, H., Wesenberg, F., Tryggvadottir, L., Malila, N., Boice, J.D., Hasle, H., Winther, J.F., 2014, "Adult life after childhood cancer in Scandinavia:diabetes, mellitus following treatmentfor cancer in childhood", Eur J Cancer, vol. 50, no. 6, pp. 1169-1175.

Hovaldt, H.B., Andersen, I., Sandager, M., Sperling, C., Frederiksen, K., Bidstrup, P.E., Johansen, C. & Dalton, S.O. 2015, "The role of social position in anxiety and depressive symptoms among Danish cancer survivors", Acta Oncologica (Stockholm, Sweden), vol. 54, no. 5, pp. 693-703.

Hovaldt, H.B., Suppli, N.P., Olsen, M.H., Steding-Jessen, M., Hansen, D.G., Moller, H., Johansen, C. & Dalton, S.O. 2015, "Who are the cancer survivors? A nationwide study in Denmark, 1943-2010", British journal of cancer, vol. 112, no. 9, pp. 1549-1553.

Hoybye, M.T., Dalton, S.O., Deltour, I., Bidstrup, P.E., Frederiksen, K. & Johansen, C. 2010, "Effect of Internet peer-support groups on psychosocial adjustment to cancer: a randomised study", British journal of cancer, vol. 102, no. 9, pp. 1348-1354.

Huang, T.T., Chen, Y., Dietz, A.C., Yasui, Y., Donaldson, S.S., Stokes, D.C., Stovall, M., Leisenring, W.M., Sklar, C.A., Diller, L.R., Mertens, A.C., Armstrong, G.T., Green, D.M., Robison, L.L. & Ness, K.K. 2014, "Pulmonary outcomes in survivors of childhood central nervous system malignancies: a report from the Childhood Cancer Survivor Study", Pediatric blood & cancer, vol. 61, no. 2, pp. 319-325.

Hudson, M.M., Mertens, A.C., Yasui, Y., Hobbie, W., Chen, H., Gurney, J.G., Yeazel, M., Recklitis, C.J., Marina, N., Robison, L.R., Oeffinger, K.C. & Childhood Cancer Survivor Study Investigators 2003, "Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study", Jama, vol. 290, no. 12, pp. 1583-1592.

Hudson, M.M., Ness, K.K., Gurney, J.G., Mulrooney, D.A., Chemaitilly, W., Krull, K.R., Green, D.M., Armstrong, G.T., Nottage, K.A., Jones, K.E., Sklar, C.A., Srivastava, D.K. & Robison, L.L. 2013, "Clinical ascertainment of health outcomes among adults treated for childhood cancer", JAMA : the journal of the American Medical Association, vol. 309, no. 22, pp. 2371-2381.

Inaba, H., Pui C.H. 2010, "Glucocorticoid use in acute lymphoblastic leukaemia" , *Lancet Oncol*, vol. 11, no. 11, pp. 1096–1106.

Inhestern, L., Beierlein, V., Bultmann, J.C., Moller, B., Romer, G., Koch, U. & Bergelt, C. 2017, "Anxiety and depression in working-age cancer survivors: a register-based study", BMC cancer, vol. 17, no. 1, pp. 347-017-3347-9.

Jacobs, L.A. & Shulman, L.N. 2017, "Follow-up care of cancer survivors: challenges and solutions", The Lancet.Oncology, vol. 18, no. 1, pp. e19-e29.

Jacola, L.M., Edelstein, K., Liu, W., Pui, C.H., Hayashi, R., Kadan-Lottick, N.S., Srivastava, D., Henderson, T., Leisenring, W., Robison, L.L., Armstrong, G.T. & Krull, K.R. 2016, "Cognitive, behaviour, and academic functioning in adolescent and young adult survivors of childhood acute lymphoblastic leukaemia: a report from the Childhood Cancer Survivor Study", The lancet.Psychiatry, vol. 3, no. 10, pp. 965-972.

Johannsdottir, I.M., Karlstad, O., Loge, J.H., Fossa, S.D., Kiserud, C. & Skurtveit, S. 2017, "Prescriptions of Antidepressants to Survivors of Cancer in Childhood, Adolescence, and Young Adulthood: A Population-Based Study", Journal of adolescent and young adult oncology, vol. 6, no. 1, pp. 120-126.

Kadan-Lottick, N.S., Zeltzer, L.K., Liu, Q., Yasui, Y., Ellenberg, L., Gioia, G., Robison, L.L. & Krull, K.R. 2010, "Neurocognitive functioning in adult survivors of childhood non-central nervous system cancers", Journal of the National Cancer Institute, vol. 102, no. 12, pp. 881-893.

Kaemingk, K.L., Carey, M.E., Moore, I.M., Herzer, M. & Hutter, J.J. 2004, "Math weaknesses in survivors of acute lymphoblastic leukemia compared to healthy children", Child neuropsychology : a journal on normal and abnormal development in childhood and adolescence, vol. 10, no. 1, pp. 14-23.

Kahalley, L.S., Wilson, S.J., Tyc, V.L., Conklin, H.M., Hudson, M.M., Wu, S., Xiong, X., Stancel, H.H. & Hinds, P.S. 2013, "Are the psychological needs of adolescent survivors of pediatric cancer adequately identified and treated?", Psycho-oncology, vol. 22, no. 2, pp. 447-458.

Kanera, I.M., Bolman, C.A., Willems, R.A., Mesters, I. & Lechner, L. 2016, "Lifestyle-related effects of the web-based Kanker Nazorg Wijzer (Cancer Aftercare Guide) intervention for cancer survivors: a randomized controlled trial", Journal of cancer survivorship: research and practice, vol. 10, no. 5, pp. 883-897.

Kasteenpohja, T., Marttunen, M., Aalto-Setala, T., Perala, J., Saarni, S.I. & Suvisaari, J. 2015, "Treatment received and treatment adequacy of depressive disorders among young adults in Finland", BMC psychiatry, vol. 15, pp. 47-015-0427-8.

Kazak, A.E., Derosa, B.W., Schwartz, L.A., Hobbie, W., Carlson, C., Ittenbach, R.F., Mao, J.J. & Ginsberg, J.P. 2010, "Psychological outcomes and health beliefs in adolescent and young adult survivors of childhood cancer and controls", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 28, no. 12, pp. 2002-2007.

Keegan, T.H.M., Bleyer, A., Rosenberg, A.S., Li, Q. & Goldfarb, M. 2017, "Second Primary Malignant Neoplasms and Survival in Adolescent and Young Adult Cancer Survivors", JAMA oncology.

Keifer, E. & Tranel, D. 2013, "A neuropsychological investigation of the Delis-Kaplan Executive Function System", Journal of clinical and experimental neuropsychology, vol. 35, no. 10, pp. 1048-1059.

Kero, A.E., Jarvela, L.S., Arola, M., Malila, N., Madanat-Harjuoja, L.M., Matomaki, J. & Lahteenmaki, P.M. 2013, "Cardiovascular morbidity in long-term survivors of early-onset cancer: A population-based study", International journal of cancer.Journal international du cancer, .

Kero, A.E., Jarvela, L.S., Arola, M., Malila, N., Madanat-Harjuoja, L.M., Matomaki, J. & Lahteenmaki, P.M. 2015, "Late mortality among 5-year survivors of early onset cancer: a population-based register study", International journal of cancer, vol. 136, no. 7, pp. 1655-1664.

Kessler, R.C., Demler, O., Frank, R.G., Olfson, M., Pincus, H.A., Walters, E.E., Wang, P., Wells, K.B. & Zaslavsky, A.M. 2005, "Prevalence and treatment of mental disorders, 1990 to 2003", The New England journal of medicine, vol. 352, no. 24, pp. 2515-2523.

Kessler, R.C., van Loo, H.M., Wardenaar, K.J., Bossarte, R.M., Brenner, L.A., Cai, T., Ebert, D.D., Hwang, I., Li, J., de Jonge, P., Nierenberg, A.A., Petukhova, M.V., Rosellini, A.J., Sampson, N.A., Schoevers, R.A., Wilcox, M.A. & Zaslavsky, A.M. 2016, "Testing a machine-learning algorithm to predict the persistence and severity of major depressive disorder from baseline self-reports", Molecular psychiatry, .

Kessler, R.C. & Wang, P.S. 2008, "The descriptive epidemiology of commonly occurring mental disorders in the United States", Annual Review of Public Health, vol. 29, pp. 115-129.

Khan, N.F., Ward, A.M., Watson, E. & Rose, P.W. 2010a and b, "Consulting and prescribing behaviour for anxiety and depression in long-term survivors of cancer in the UK", European journal of cancer (Oxford, England : 1990), vol. 46, no. 18, pp. 3339-3344.

Kieran, M.W., Walker, D., Frappaz, D. & Prados, M. 2010, "Brain tumors: from childhood through adolescence into adulthood", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 28, no. 32, pp. 4783-4789.

King, A.A., Seidel, K., Di, C., Leisenring, W.M., Perkins, S.M., Krull, K.R., Sklar, C.A., Green, D.M., Armstrong, G.T., Zeltzer, L.K., Wells, E., Stovall, M., Ullrich, N.J., Oeffinger, K.C., Robison, L.L. & Packer, R.J. 2017, "Long-term neurologic health and psychosocial function of adult survivors of childhood medulloblastoma/PNET: a report from the Childhood Cancer Survivor Study", Neuro-oncology, vol. 19, no. 5, pp. 689-698.

Kirchhoff, A.C., Krull, K.R., Ness, K.K., Armstrong, G.T., Park, E.R., Stovall, M., Robison, L.L. & Leisenring, W. 2011, "Physical, mental, and neurocognitive status and employment outcomes in the childhood cancer survivor study cohort", Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, vol. 20, no. 9, pp. 1838-1849.

Koch, S.V., Kejs, A.M., Engholm, G., Johansen, C. & Schmiegelow, K. 2004, "Educational attainment among survivors of childhood cancer: a population-based cohort study in Denmark", British journal of cancer, vol. 91, no. 5, pp. 923-928.

Koch, S.V., Kejs, A.M., Engholm, G., Moller, H., Johansen, C. & Schmiegelow, K. 2011, "Marriage and divorce among childhood cancer survivors", Journal of pediatric hematology/oncology, vol. 33, no. 7, pp. 500-505.

Koehler P.J., 1995, “Use of corticosteroids in neuro-oncology”, *Anticancer Drugs,* vol. 6, no. 1, pp. 19–33.

Konrad, K., Firk, C. & Uhlhaas, P.J. 2013, "Brain development during adolescence: neuroscientific insights into this developmental period", Deutsches Arzteblatt international, vol. 110, no. 25, pp. 425-431.

Kopp, L.M., Gastelum, Z., Guerrero, C.H., Howe, C.L., Hingorani, P., Hingle, M. 2017, “Lifestyle behavior interventions delivered using technology in childhood, adolescent, and young adult cancer survivors: A systematic review”, Pediatr Blood Cancer, vol. 64, no.1, pp.13-17.

Kremer, L.C., Mulder, R.L., Oeffinger, K.C., Bhatia, S., Landier, W., Levitt, G., Constine, L.S., Wallace, W.H., Caron, H.N., Armenian, S.H., Skinner, R., Hudson, M.M. & International Late Effects of Childhood Cancer Guideline Harmonization Group 2013, "A worldwide collaboration to harmonize guidelines for the long-term follow-up of childhood and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group", Pediatric blood & cancer, vol. 60, no. 4, pp. 543-549.

Kroenke, K., Theobald, D., Wu, J., Norton, K., Morrison, G., Carpenter, J. & Tu, W. 2010, "Effect of telecare management on pain and depression in patients with cancer: a randomized trial", Jama, vol. 304, no. 2, pp. 163-171.

Krull, K.R., Hockenberry, M.J., Miketova, P., Carey, M. & Moore, I.M. 2013b, "Chemotherapy-related changes in central nervous system phospholipids and neurocognitive function in childhood acute lymphoblastic leukemia", Leukemia & lymphoma, vol. 54, no. 3, pp. 535-540.

Krull, K.R., Minoshima, S., Edelmann, M., Morris, B., Sabin, N.D., Brinkman, T.M., Armstrong, G.T., Robison, L.L., Hudson, M.M. & Shulkin, B. 2014, "Regional brain glucose metabolism and neurocognitive function in adult survivors of childhood cancer treated with cranial radiation", Journal of nuclear medicine : official publication, Society of Nuclear Medicine, vol. 55, no. 11, pp. 1805-1810.

Krull, K.R., Sabin, N.D., Reddick, W.E., Zhu, L., Armstrong, G.T., Green, D.M., Arevalo, A.R., Krasin, M.J., Srivastava, D.K., Robison, L.L. & Hudson, M.M. 2012, "Neurocognitive function and CNS integrity in adult survivors of childhood hodgkin lymphoma", Journal of clinical oncology : official

journal of the American Society of Clinical Oncology, vol. 30, no. 29, pp. 3618-3624.

Kuijpers, W., Groen, W.G., Loos, R., Oldenburg, H.S., Wouters, M.W., Aaronson, N.K. & van Harten, W.H. 2015, "An interactive portal to empower cancer survivors: a qualitative study on user expectations", Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, vol. 23, no. 9, pp. 2535-2542.

Kuehni, C.E., Strippoli, M.P., Rueegg, C.S., Rebholz, C.E., Bergstraesser, E., Grotzer, M., von der Weid, N.X., Michel, G. & Swiss Pediatric Oncology Group (SPOG) 2012, "Educational achievement in Swiss childhood cancer survivors compared with the general population", Cancer, vol. 118, no. 5, pp. 1439-1449.

Kunin-Batson, A., Kadan-Lottick, N. & Neglia, J.P. 2014, "The contribution of neurocognitive functioning to quality of life after childhood acute lymphoblastic leukemia", Psycho-oncology, .

Kunin-Batson, A.S., Lu, X., Balsamo, L., Graber, K., Devidas, M., Hunger, S.P., Carroll, W.L., Winick, N.J., Mattano, L.A.,Jr, Maloney, K.W. & Kadan-Lottick, N.S. 2016, "Prevalence and predictors of anxiety and depression after completion of chemotherapy for childhood acute lymphoblastic leukemia: A prospective longitudinal study", Cancer, vol. 122, no. 10, pp. 1608-1617.

Kunin-Batson, A., Steele, J., Mertens, A. & Neglia, J.P. 2016, "A randomized controlled pilot trial of a Web-based resource to improve cancer knowledge in adolescent and young adult survivors of childhood cancer", Psycho-oncology, vol. 25, no. 11, pp. 1308-1316.

Kurtz, B.P. & Abrams, A.N. 2011, "Psychiatric aspects of pediatric cancer", Pediatric clinics of North America, vol. 58, no. 4, pp. 1003-23, xii.

Kwak, M., Zebrack, B.J., Meeske, K.A., Embry, L., Aguilar, C., Block, R., Hayes-Lattin, B., Li, Y., Butler, M. & Cole, S. 2013, "Prevalence and predictors of post-traumatic stress symptoms in adolescent and young adult cancer survivors: a 1-year follow-up study", Psycho-oncology, vol. 22, no. 8, pp. 1798-1806.

Lahteenmaki, P.M., Harila-Saari, A., Pukkala, E.I., Kyyronen, P., Salmi, T.T. & Sankila, R. 2007, "Scholastic achievements of children with brain tumors at the end of comprehensive education: a nationwide, register-based study", Neurology, vol. 69, no. 3, pp. 296-305.

Lahteenmaki, P.M., Salmi, H.A., Salmi, T.T., Helenius, H., Makipernaa, A., Lanning, M., Perkkio, M. & Siimes, M.A. 1999, "Military service of male survivors of childhood malignancies", Cancer, vol. 85, no. 3, pp. 732-740.

Lahteenmaki, P.M., Sankila, R., Pukkala, E., Kyyronen, P. & Harila-Saari, A. 2008, "Scholastic achievement of children with lymphoma or Wilms tumor at the end of comprehensive education--a nationwide, register-based study", International journal of cancer.Journal international du cancer, vol. 123, no. 10, pp. 2401-2405.

Lancashire, E.R., Frobisher, C., Reulen, R.C., Winter, D.L., Glaser, A. & Hawkins, M.M. 2010, "Educational attainment among adult survivors of childhood cancer in Great Britain: a population-based cohort study", Journal of the National Cancer Institute, vol. 102, no. 4, pp. 254-270.

Landier, W., Bhatia, S., Eshelman, D.A., Forte, K.J., Sweeney, T., Hester, A.L., Darling, J., Armstrong, F.D., Blatt, J., Constine, L.S., Freeman, C.R., Friedman, D.L., Green, D.M., Marina, N., Meadows, A.T., Neglia, J.P., Oeffinger, K.C., Robison, L.L., Ruccione, K.S., Sklar, C.A. & Hudson, M.M. 2004, "Development of risk-based guidelines for pediatric cancer survivors: the Children's Oncology Group Long-Term Follow-Up Guidelines from the Children's Oncology Group Late Effects Committee and Nursing Discipline", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 22, no. 24, pp. 4979-4990.

Landier, W., Chen, Y., Namdar, G., Francisco, L., Wilson, K., Herrera, C., Armenian, S., Wolfson, J.A., Sun, C.L., Wong, F.L. & Bhatia, S. 2015, "Impact of Tailored Education on Awareness of Personal Risk for Therapy-Related Complications Among Childhood Cancer Survivors", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 33, no. 33, pp. 3887-3893.

Landier, W., Knight, K., Wong, F.L., Lee, J., Thomas, O., Kim, H., Kreissman, S.G., Schmidt, M.L., Chen, L., London, W.B., Gurney, J.G. & Bhatia, S. 2014, "Ototoxicity in children with high-risk neuroblastoma: prevalence, risk factors, and concordance of grading scales--a report from the Children's Oncology Group", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 32, no. 6, pp. 527-534.

Leger, K., Slone, T., Lemler, M., Leonard, D., Cochran, C., Bowman, W.P., Bashore, L. & Winick, N. 2015, "Subclinical cardiotoxicity in childhood cancer survivors exposed to very low dose anthracycline therapy", Pediatric blood & cancer, vol. 62, no. 1, pp. 123-127.

Leinonen, M.K., Miettinen, J., Heikkinen, S., Pitkaniemi, J. & Malila, N. 2017, "Quality measures of the population-based Finnish Cancer Registry indicate sound data quality for solid malignant tumours", European journal of cancer (Oxford, England : 1990), vol. 77, pp. 31-39.

Leisenring, W.M., Mertens, A.C., Armstrong, G.T., Stovall, M.A., Neglia, J.P., Lanctot, J.Q., Boice, J.D.,Jr, Whitton, J.A. & Yasui, Y. 2009, "Pediatric cancer survivorship research: experience of the Childhood Cancer Survivor Study", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 27, no. 14, pp. 2319-2327.

Linde, K., Kriston, L., Rucker, G., Jamil, S., Schumann, I., Meissner, K., Sigterman, K. & Schneider, A. 2015, "Efficacy and acceptability of pharmacological treatments for depressive disorders in primary care: systematic review and network meta-analysis", Annals of family medicine, vol. 13, no. 1, pp. 69-79.

Lindell, R.B., Koh, S.J., Alvarez, J.M., Koyama, T., Esbenshade, A.J., Simmons, J.H. & Friedman, D.L. 2015, "Knowledge of diagnosis, treatment history, and risk of late effects among childhood cancer survivors and parents: The impact of a survivorship

clinic", Pediatric blood & cancer, vol. 62, no. 8, pp. 1444-1451.

Lipshultz, S.E., Landy, D.C., Lopez-Mitnik, G., Lipsitz, S.R., Hinkle, A.S., Constine, L.S., French, C.A., Rovitelli, A.M., Proukou, C., Adams, M.J. & Miller, T.L. 2012, "Cardiovascular status of childhood cancer survivors exposed and unexposed to cardiotoxic therapy", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 30, no. 10, pp. 1050-1057.

Lorenzi, M., McMillan, A.J., Siegel, L.S., Zumbo, B.D., Glickman, V., Spinelli, J.J., Goddard, K.J., Pritchard, S.L., Rogers, P.C. & McBride, M.L. 2009, "Educational outcomes among survivors of childhood cancer in British Columbia, Canada: report of the Childhood/Adolescent/Young Adult Cancer Survivors (CAYACS) Program", Cancer, vol. 115, no. 10, pp. 2234-2245.

Lund, B., Asberg, A., Heyman, M., Kanerva, J., Harila-Saari, A., Hasle, H., Soderhall, S., Jonsson, O.G., Lydersen, S., Schmiegelow, K. & Nordic Society of Paediatric Haematology and Oncology 2011a, "Risk factors for treatment related mortality in childhood acute lymphoblastic leukaemia", Pediatric blood & cancer, vol. 56, no. 4, pp. 551-559.

Lund, L.W., Schmiegelow, K., Rechnitzer, C. & Johansen, C. 2011b, "A systematic review of studies on psychosocial late effects of childhood cancer: structures of society and methodological pitfalls may challenge the conclusions", Pediatric blood & cancer, vol. 56, no. 4, pp. 532-543.

Lund, L.W., Winther, J.F., Cederkvist, L., Andersen, K.K., Dalton, S.O., Appel, C.W., Rechnitzer, C., Schmiegelow, K. & Johansen, C. 2015, "Increased risk of antidepressant use in childhood cancer survivors: a Danish population-based cohort study", European journal of cancer (Oxford, England : 1990), vol. 51, no. 5, pp. 675-684.

Lund, L.W., Winther, J.F., Dalton, S.O., Cederkvist, L., Jeppesen, P., Deltour, I., Hargreave, M., Kjaer, S.K., Jensen, A., Rechnitzer, C., Andersen, K.K., Schmiegelow, K. & Johansen, C. 2013, "Hospital contact for mental disorders in survivors of childhood cancer and their siblings in Denmark: a population-based cohort study", The Lancet.Oncology, vol. 14, no. 10, pp. 971-980.

Maass, S.W., Roorda, C., Berendsen, A.J., Verhaak, P.F. & de Bock, G.H. 2015a, "The prevalence of long-term symptoms of depression and anxiety after breast cancer treatment: A systematic review", Maturitas, vol. 82, no. 1, pp. 100-108.

Maass, S.W., Roorda, C., Berendsen, A.J., Verhaak, P.F. & de Bock, G.H. 2015b, "The prevalence of long-term symptoms of depression and anxiety after breast cancer treatment: A systematic review", Maturitas, vol. 82, no. 1, pp. 100-108.

Machann, W., Beer, M., Breunig, M., Stork, S., Angermann, C., Seufert, I., Schwab, F., Kolbl, O., Flentje, M. & Vordermark, D. 2011, "Cardiac magnetic resonance imaging findings in 20-year survivors of mediastinal radiotherapy for Hodgkin's disease", International journal of radiation oncology, biology, physics, vol. 79, no. 4, pp. 1117-1123.

Madanat-Harjuoja, L.M., Lahteenmaki, P.M., Hurme, S., Dyba, T., Salmi, T.T., Sankila, R. 2008,"Hypothyroidism among pediatric cancer patients: A nationwide, registry-based study", Int J Cancer, vol. 122, no. 8, pp. 1868-1872.

Madanat-Harjuoja, L.M., Pokhrel, A., Kivivuori, S.M. & Saarinen-Pihkala, U.M. 2014, "Childhood cancer survival in Finland (1953-2010): a nation-wide population-based study", International journal of cancer, vol. 135, no. 9, pp. 2129-2134.

Mahoney, D.H.,Jr, Shuster, J.J., Nitschke, R., Lauer, S.J., Steuber, C.P., Winick, N. & Camitta, B. 1998, "Acute neurotoxicity in children with B-precursor acute lymphoid leukemia: an association with intermediate-dose intravenous methotrexate and intrathecal triple therapy--a Pediatric Oncology Group study", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 16, no. 5, pp. 1712-1722.

Mendoza, J.A., Baker, K.S., Moreno, M.A., Whitlock, K., Abbey-Lambertz, M., Waite, A., Colburn, T. & Chow, E.J. 2017, "A Fitbit and Facebook mHealth intervention for promoting physical activity among adolescent and young adult childhood cancer survivors: A pilot study", Pediatric blood & cancer, vol. 64, no. 12, pp. 10.1002/pbc.26660. Epub 2017 Jun 15.

Mertens, A.C., Liu, Q., Neglia, J.P., Wasilewski, K., Leisenring, W., Armstrong, G.T., Robison, L.L. & Yasui, Y. 2008, "Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study", Journal of the National Cancer Institute, vol. 100, no. 19, pp. 1368-1379.

Mertens, A.C., Yasui, Y., Liu, Y., Stovall, M., Hutchinson, R., Ginsberg, J., Sklar, C., Robison, L.L. & Childhood Cancer Survivor Study 2002, "Pulmonary complications in survivors of childhood and adolescent cancer. A report from the Childhood Cancer Survivor Study", Cancer, vol. 95, no. 11, pp. 2431-2441.

Michel, G., Rebholz, C.E., von der Weid, N.X., Bergstraesser, E. & Kuehni, C.E. 2010, "Psychological distress in adult survivors of childhood cancer: the Swiss Childhood Cancer Survivor study", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 28, no. 10, pp. 1740-1748.

Milam, J., Slaughter, R., Meeske, K., Ritt-Olson, A., Sherman-Bien, S., Freyer, D.R., Kuperberg, A. & Hamilton, A.S. 2016, "Substance use among adolescent and young adult cancer survivors", Psycho-oncology, vol. 25, no. 11, pp. 1357-1362.

Miller, A.M., Lopez-Mitnik, G., Somarriba, G., Lipsitz, S.R., Hinkle, A.S., Constine, L.S., Lipshultz, S.E. & Miller, T.L. 2013, "Exercise capacity in long-term survivors of pediatric cancer: an analysis from the Cardiac Risk Factors in Childhood Cancer Survivors Study", Pediatric blood & cancer, vol. 60, no. 4, pp. 663-668.

Mitby, P.A., Robison, L.L., Whitton, J.A., Zevon, M.A., Gibbs, I.C., Tersak, J.M., Meadows, A.T., Stovall, M., Zeltzer, L.K., Mertens, A.C. & Childhood Cancer Survivor Study Steering Committee 2003, "Utilization of special education services and

educational attainment among long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study", Cancer, vol. 97, no. 4, pp. 1115-1126.

Moller, T.R., Garwicz, S., Barlow, L., Winther, J.F., Glattre, E., Olafsdottir, G., Olsen, J.H., Perfekt, R., Ritvanen, A., Sankila, R., Tulinius, H., Association of the Nordic Cancer Registries & Nordic Society for Pediatric Hematology and Oncology 2001, "Decreasing late mortality among five-year survivors of cancer in childhood and adolescence: a population-based study in the Nordic countries", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 19, no. 13, pp. 3173-3181.

Monje, M., Thomason, M.E., Rigolo, L., Wang, Y., Waber, D.P., Sallan, S.E. & Golby, A.J. 2013, "Functional and structural differences in the hippocampus associated with memory deficits in adult survivors of acute lymphoblastic leukemia", Pediatric blood & cancer, vol. 60, no. 2, pp. 293-300.

Moore, I.M., Hockenberry, M.J., Anhalt, C., McCarthy, K. & Krull, K.R. 2012, "Mathematics intervention for prevention of neurocognitive deficits in childhood leukemia", Pediatric blood & cancer, vol. 59, no. 2, pp. 278-284.

Moore, M., Yuen, H.M., Dunn, N., Mullee, M.A., Maskell, J. & Kendrick, T. 2009, "Explaining the rise in antidepressant prescribing: a descriptive study using the general practice research database", BMJ (Clinical research ed.), vol. 339, pp. b3999.

Morris, B., Partap, S., Yeom, K., Gibbs, I.C., Fisher, P.G. & King, A.A. 2009, "Cerebrovascular disease in childhood cancer survivors: A Children's Oncology Group Report", Neurology, vol. 73, no. 22, pp. 1906-1913.

Mulrooney, D.A., Armstrong, G.T., Huang, S., Ness, K.K., Ehrhardt, M.J., Joshi, V.M., Plana, J.C., Soliman, E.Z., Green, D.M., Srivastava, D., Santucci, A., Krasin, M.J., Robison, L.L. & Hudson, M.M. 2016, "Cardiac Outcomes in Adult Survivors of Childhood Cancer Exposed to Cardiotoxic Therapy: A Cross-sectional Study", Annals of Internal Medicine, vol. 164, no. 2, pp. 93-101.

Munk-Jorgensen, P. & Ostergaard, S.D. 2011, "Register-based studies of mental disorders", Scandinavian Journal of Public Health, vol. 39, no. 7 Suppl, pp. 170-174.

Myers, R.M., Balsamo, L., Lu, X., Devidas, M., Hunger, S.P., Carroll, W.L., Winick, N.J., Maloney, K.W. & Kadan-Lottick, N.S. 2014, "A prospective study of anxiety, depression, and behavioral changes in the first year after a diagnosis of childhood acute lymphoblastic leukemia: a report from the Children's Oncology Group", Cancer, vol. 120, no. 9, pp. 1417-1425.

Nagarajan, R., Clohisy, D.R., Neglia, J.P., Yasui, Y., Mitby, P.A., Sklar, C., Finklestein, J.Z., Greenberg, M., Reaman, G.H., Zeltzer, L. & Robison, L.L. 2004, "Function and quality-of-life of survivors of pelvic and lower extremity osteosarcoma and Ewing's sarcoma: the Childhood Cancer Survivor Study", British journal of cancer, vol. 91, no. 11, pp. 1858-1865.

Nathan, P.C., Daugherty, C.K., Wroblewski, K.E., Kigin, M.L., Stewart, T.V., Hlubocky, F.J., Grunfeld, E., Del Giudice, M.E., Ward, L.A., Galliher, J.M., Oeffinger, K.C. & Henderson, T.O. 2013, "Family physician preferences and knowledge gaps regarding the care of adolescent and young adult survivors of childhood cancer", Journal of cancer survivorship : research and practice, vol. 7, no. 3, pp. 275-282.

Nathan, P.C., Ness, K.K., Greenberg, M.L., Hudson, M., Wolden, S., Davidoff, A., Laverdiere, C., Mertens, A., Whitton, J., Robison, L.L., Zeltzer, L. & Gurney, J.G. 2007, "Health-related quality of life in adult survivors of childhood Wilms tumor or neuroblastoma: A report from the childhood cancer survivor study", Pediatric blood & cancer, vol. 49, no. 5, pp. 704-715.

Nathan, P.C., Patel, S.K., Dilley, K., Goldsby, R., Harvey, J., Jacobsen, C., Kadan-Lottick, N., McKinley, K., Millham, A.K., Moore, I., Okcu, M.F., Woodman, C.L., Brouwers, P., Armstrong, F.D. & Children's Oncology Group Long-term Follow-up Guidelines Task Force on Neurocognitive/Behavioral Complications After Childhood Cancer 2007, "Guidelines for identification of, advocacy for, and intervention in neurocognitive problems in survivors of childhood cancer: a report from the Children's Oncology Group", Archives of Pediatrics & Adolescent Medicine, vol. 161, no. 8, pp. 798-806.

Ness, K.K., DeLany, J.P., Kaste, S.C., Mulrooney, D.A., Pui, C.H., Chemaitilly, W., Karlage, R.E., Lanctot, J.Q., Howell, C.R., Lu, L., Srivastava, D.K., Robison, L.L. & Hudson, M.M. 2015, "Energy balance and fitness in adult survivors of childhood acute lymphoblastic leukemia", Blood, vol. 125, no. 22, pp. 3411-3419.

Ness, K.K., Hudson, M.M., Ginsberg, J.P., Nagarajan, R., Kaste, S.C., Marina, N., Whitton, J., Robison, L.L. & Gurney, J.G. 2009, "Physical performance limitations in the Childhood Cancer Survivor Study cohort", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 27, no. 14, pp. 2382-2389.

Ness, K.K., Morris, E.B., Nolan, V.G., Howell, C.R., Gilchrist, L.S., Stovall, M., Cox, C.L., Klosky, J.L., Gajjar, A. & Neglia, J.P. 2010, "Physical performance limitations among adult survivors of childhood brain tumors", Cancer, vol. 116, no. 12, pp. 3034-3044.

Netson, K.L., Conklin, H.M., Wu, S., Xiong, X. & Merchant, T.E. 2013, "Longitudinal investigation of adaptive functioning following conformal irradiation for pediatric craniopharyngioma and low-grade glioma", International journal of radiation oncology, biology, physics, vol. 85, no. 5, pp. 1301-1306.

Odame, I., Duckworth, J., Talsma, D., Beaumont, L., Furlong, W., Webber, C. & Barr, R. 2006, "Osteopenia, physical activity and health-related quality of life in survivors of brain tumors treated in childhood", Pediatric blood & cancer, vol. 46, no. 3, pp. 357-362.

Oeffinger, K.C., Mertens, A.C., Sklar, C.A., Kawashima, T., Hudson, M.M., Meadows, A.T., Friedman, D.L., Marina, N., Hobbie, W., Kadan-Lottick, N.S., Schwartz, C.L., Leisenring, W., Robison, L.L. & Childhood Cancer Survivor Study 2006, "Chronic health conditions in adult survivors of childhood

cancer", The New England journal of medicine, vol. 355, no. 15, pp. 1572-1582.

Ostuzzi, G., Benda, L., Costa, E. & Barbui, C. 2015, "Efficacy and acceptability of antidepressants on the continuum of depressive experiences in patients with cancer: Systematic review and meta-analysis", Cancer treatment reviews, vol. 41, no. 8, pp. 714-724.

Ottaviani, G., Robert, R.S., Huh, W.W., Palla, S. & Jaffe, N. 2013, "Sociooccupational and physical outcomes more than 20 years after the diagnosis of osteosarcoma in children and adolescents: limb salvage versus amputation", Cancer, vol. 119, no. 20, pp. 3727-3736.

Packer, R.J., Gurney, J.G., Punyko, J.A., Donaldson, S.S., Inskip, P.D., Stovall, M., Yasui, Y., Mertens, A.C., Sklar, C.A., Nicholson, H.S., Zeltzer, L.K., Neglia, J.P. & Robison, L.L. 2003, "Long-term neurologic and neurosensory sequelae in adult survivors of a childhood brain tumor: childhood cancer survivor study", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 21, no. 17, pp. 3255-3261.

Packer, R.J., Littman, P.A., Sposto, R.M., D'Angio, G., Priest, J.R., Heideman, R.L., Bruce, D.A. & Nelson, D.F. 1987, "Results of a pilot study of hyperfractionated radiation therapy for children with brain stem gliomas", International journal of radiation oncology, biology, physics, vol. 13, no. 11, pp. 1647-1651.

Packer, R.J., Sutton, L.N., Atkins, T.E., Radcliffe, J., Bunin, G.R., D'Angio, G., Siegel, K.R. & Schut, L. 1989, "A prospective study of cognitive function in children receiving whole-brain radiotherapy and chemotherapy: 2-year results", Journal of neurosurgery, vol. 70, no. 5, pp. 707-713.

Pan, X. & Sambamoorthi, U. 2015, "Health care expenditures associated with depression in adults with cancer", The Journal of community and supportive oncology, vol. 13, no. 7, pp. 240-247.

Pang, J.W., Friedman, D.L., Whitton, J.A., Stovall, M., Mertens, A.C., Robison, L.L. & Weiss, N.S. 2008, "Employment status among adult survivors in the Childhood Cancer Survivor Study", Pediatric blood & cancer, vol. 50, no. 1, pp. 104-110.

Patel, S.K., Katz, E.R., Richardson, R., Rimmer, M. & Kilian, S. 2009, "Cognitive and problem solving training in children with cancer: a pilot project", Journal of pediatric hematology/oncology, vol. 31, no. 9, pp. 670-677.

Pearson, S.A., Abrahamowicz, M., Srasuebkul, P. & Buckley, N.A. 2015, "Antidepressant therapy in cancer patients: initiation and factors associated with treatment", Pharmacoepidemiology and drug safety, vol. 24, no. 6, pp. 600-609.

Petersen, I.C., Spix, P., Kaatsch, N., Graf, G., Janka and R Kollek, 2013, "Parental informed consent in pediatric cancer trials: a population-based survey in Germany", Pediatr Blood Cancer, vol. 52, no. 7, pp. 853-859.

Pirkola, S.P., Isometsa, E., Suvisaari, J., Aro, H., Joukamaa, M., Poikolainen, K., Koskinen, S., Aromaa, A. & Lonnqvist, J.K. 2005, "DSM-IV mood-, anxiety- and alcohol use disorders and their comorbidity in the Finnish general population--results from the Health 2000 Study", Social psychiatry and psychiatric epidemiology, vol. 40, no. 1, pp. 1-10.

Pirl, W.F., Greer, J., Temel, J.S., Yeap, B.Y. & Gilman, S.E. 2009, "Major depressive disorder in long-term cancer survivors: analysis of the National Comorbidity Survey Replication", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 27, no. 25, pp. 4130-4134.

Piscione, P.J., Bouffet, E., Timmons, B., Courneya, K.S., Tetzlaff, D., Schneiderman, J.E., de Medeiros, C.B., Bartels, U. & Mabbott, D.J. 2017, "Exercise training improves physical function and fitness in long-term paediatric brain tumour survivors treated with cranial irradiation", European journal of cancer (Oxford, England : 1990), vol. 80, pp. 63-72.

Prasad, P.K., Hardy, K.K., Zhang, N., Edelstein, K., Srivastava, D., Zeltzer, L., Stovall, M., Seibel, N.L., Leisenring, W., Armstrong, G.T., Robison, L.L. & Krull, K. 2015, "Psychosocial and Neurocognitive Outcomes in Adult Survivors of Adolescent and Early Young Adult Cancer: A Report From the Childhood Cancer Survivor Study", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 33, no. 23, pp. 2545-2552.

Prasad, P.K., Signorello, L.B., Friedman, D.L., Boice, J.D.,Jr & Pukkala, E. 2012, "Long-term non-cancer mortality in pediatric and young adult cancer survivors in Finland", Pediatric blood & cancer, vol. 58, no. 3, pp. 421-427.

Primus, R.J. & Kellogg, C.K. 1990, "Gonadal hormones during puberty organize environment-related social interaction in the male rat", Hormones and behavior, vol. 24, no. 3, pp. 311-323.

Pui, C.H. 2009, "Prophylactic cranial irradiation: going, going, gone", The Lancet.Oncology, vol. 10, no. 10, pp. 932-933.

Rabin, C. & Politi, M. 2010, "Need for health behavior interventions for young adult cancer survivors", American Journal of Health Behavior, vol. 34, no. 1, pp. 70-76.

Raj, S.P., Narad, M.E., Salloum, R., Platt, A., Thompson, A., Baum, K.T. & Wade, S.L. 2017, "Development of a Web-Based Psychosocial Intervention for Adolescent and Young Adult Survivors of Pediatric Brain Tumor", Journal of adolescent and young adult oncology, .

Rebholz, C.E., Kuehni, C.E., Strippoli, M.P., Rueegg, C.S., Michel, G., Hengartner, H., Bergstraesser, E., von der Weid, N.X. & Swiss Pediatric Oncology Group (SPOG) 2012, "Alcohol consumption and binge drinking in young adult childhood cancer survivors", Pediatric blood & cancer, vol. 58, no. 2, pp. 256-264.

Reddick, W.E., Taghipour, D.J., Glass, J.O., Ashford, J., Xiong, X., Wu, S., Bonner, M., Khan, R.B. & Conklin, H.M. 2014, "Prognostic factors that increase the risk for reduced white matter volumes and deficits in attention and learning for survivors of childhood cancers", Pediatric blood & cancer, vol. 61, no. 6, pp. 1074-1079.

Reimers, T.S., Mortensen, E.L. & Schmiegelow, K. 2007, "Memory deficits in long-term survivors of

childhood brain tumors may primarily reflect general cognitive dysfunctions", Pediatric blood & cancer, vol. 48, no. 2, pp. 205-212.

Reimers, T.S., Ehrenfels, S., Mortensen, E.L., Schmiegelow, M., Sonderkaer, S., Carstensen, H., Schmiegelow, K. & Muller, J. 2003, "Cognitive deficits in long-term survivors of childhood brain tumors: Identification of predictive factors", Medical and pediatric oncology, vol. 40, no. 1, pp. 26-34.

Reulen, R.C., Winter, D.L., Frobisher, C., Lancashire, E.R., Stiller, C.A., Jenney, M.E., Skinner, R., Stevens, M.C., Hawkins, M.M. & British Childhood Cancer Survivor Study Steering Group 2010, "Long-term cause-specific mortality among survivors of childhood cancer", Jama, vol. 304, no. 2, pp. 172-179.

Robison, L.L., Armstrong, G.T., Boice, J.D., Chow, E.J., Davies, S.M., Donaldson, S.S., Green, D.M., Hammond, S., Meadows, A.T., Mertens, A.C., Mulvihill, J.J., Nathan, P.C., Neglia, J.P., Packer, R.J., Rajaraman, P., Sklar, C.A., Stovall, M., Strong, L.C., Yasui, Y., Zeltzer, L.K.2009, "Childhood Cancer Survivor Study: a National Cancer Institute-supported resource for outcome and intervention research", Journal of Clinical Oncology, vol. 27, no.14, pp. 2308-2318.

Robison, L.L., Hudson, M.M. 2014, "Survivors of childhood and adolescent cancer: life-long risks and responsibilities", *Nat Rev Cancer,* vol. 14, no. 1, pp. 61-70.

Roerink, S.H., de Ridder, M., Prins, J., Huijbers, A., de Wilt, H.J., Marres, H., Repping-Wuts, H., Stikkelbroeck, N.M., Timmers, H.J., Hermus, A.R. & Netea-Maier, R.T. 2013, "High level of distress in long-term survivors of thyroid carcinoma: results of rapid screening using the distress thermometer", Acta Oncologica (Stockholm, Sweden), vol. 52, no. 1, pp. 128-137.

Ross, L., Johansen, C., Dalton, S.O., Mellemkjaer, L., Thomassen, L.H., Mortensen, P.B. & Olsen, J.H. 2003, "Psychiatric hospitalizations among survivors of cancer in childhood or adolescence", The New England journal of medicine, vol. 349, no. 7, pp. 650-657.

Ross, J.A., Oeffinger, K.C., Davies, S.M., Mertens, A.C., Langer, E.K., Kiffmeyer, W.R., Sklar, C.A., Stovall, M., Yasui, Y. & Robison, L.L. 2004, "Genetic variation in the leptin receptor gene and obesity in survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 22, no. 17, pp. 3558-3562.

Rourke, M.T., Hobbie, W.L., Schwartz, L. & Kazak, A.E. 2007, "Posttraumatic stress disorder (PTSD) in young adult survivors of childhood cancer", Pediatric blood & cancer, vol. 49, no. 2, pp. 177-182.

Ruland, C.M., Andersen, T., Jeneson, A., Moore, S., Grimsbo, G.H., Borosund, E. & Ellison, M.C. 2013, "Effects of an internet support system to assist cancer patients in reducing symptom distress: a randomized controlled trial", Cancer nursing, vol. 36, no. 1, pp. 6-17.

Salem, H., Johansen, C., Schmiegelow, K., Winther, J.F., Wehner, P.S., Hasle, H., Rosthoj, S., Kazak, A.E. & E Bidstrup, P. 2017, "FAMily-Oriented Support (FAMOS): development and feasibility of a psychosocial intervention for families of childhood cancer survivors", Acta Oncologica (Stockholm, Sweden), vol. 56, no. 2, pp. 367-374.

Salz, T., Baxi, S.S., Raghunathan, N., Onstad, E.E., Freedman, A.N., Moskowitz, C.S., Dalton, S.O., Goodman, K.A., Johansen, C., Matasar, M.J., de Nully Brown, P., Oeffinger, K.C. & Vickers, A.J. 2015, "Are we ready to predict late effects? A systematic review of clinically useful prediction models", European journal of cancer (Oxford, England : 1990), vol. 51, no. 6, pp. 758-766.

Schmidt, M.E., Wiskemann, J., Ulrich, C.M., Schneeweiss, A. & Steindorf, K. 2017, "Self-reported physical activity behavior of breast cancer survivors during and after adjuvant therapy: 12 months follow-up of two randomized exercise intervention trials", Acta Oncologica (Stockholm, Sweden), vol. 56, no. 4, pp. 618-627.

Schuitema, I., Deprez, S., Van Hecke, W., Daams, M., Uyttebroeck, A., Sunaert, S., Barkhof, F., van Dulmen-den Broeder, E., van der Pal, H.J., van den Bos, C., Veerman, A.J. & de Sonneville, L.M. 2013, "Accelerated aging, decreased white matter integrity, and associated neuropsychological dysfunction 25 years after pediatric lymphoid malignancies", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 31, no. 27, pp. 3378-3388.

Schultz, K.A., Ness, K.K., Whitton, J., Recklitis, C., Zebrack, B., Robison, L.L., Zeltzer, L. & Mertens, A.C. 2007, "Behavioral and social outcomes in adolescent survivors of childhood cancer: a report from the childhood cancer survivor study", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 25, no. 24, pp. 3649-3656.

Schultz, S.L., Dalton, S.O., Christensen, J., Carlsen, K., Ross, L. & Johansen, C. 2011, "Factors correlated with fatigue in breast cancer survivors undergoing a rehabilitation course, Denmark, 2002-2005", Psycho-oncology, vol. 20, no. 4, pp. 352-360.

Seitz, D.C., Knaevelsrud, C., Duran, G., Waadt, S. & Goldbeck, L. 2014a, "Internet-based psychotherapy in young adult survivors of pediatric cancer: feasibility and participants' satisfaction", Cyberpsychology, behavior and social networking, vol. 17, no. 9, pp. 624-629.

Seitz, D.C., Knaevelsrud, C., Duran, G., Waadt, S., Loos, S. & Goldbeck, L. 2014b, "Efficacy of an internet-based cognitive-behavioral intervention for long-term survivors of pediatric cancer: a pilot study", Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, vol. 22, no. 8, pp. 2075-2083.

Shah, S.S., Dellarole, A., Peterson, E.C., Bregy, A., Komotar, R., Harvey, P.D. & Elhammady, M.S. 2015, "Long-term psychiatric outcomes in pediatric brain tumor survivors", Child's nervous system : ChNS : official journal of the International Society for Pediatric Neurosurgery, vol. 31, no. 5, pp. 653-663.

Sharp, K.M.H., Lindwall, J.J., Willard, V.W., Long, A.M., Martin-Elbahesh, K.M. & Phipps, S. 2017, "Cancer as a stressful life event: Perceptions of children with cancer and their peers", Cancer, vol. 123, no. 17, pp. 3385-3393.

Shortman, R.I., Lowis, S.P., Penn, A., McCarter, R.J., Hunt, L.P., Brown, C.C., Stevens, M.C., Curran, A.L. & Sharples, P.M. 2014, "Cognitive function in children with brain tumors in the first year after diagnosis compared to healthy matched controls", Pediatric blood & cancer, vol. 61, no. 3, pp. 464-472.

Sieswerda, **E.**, Mulder, R.L., van Dijk, I.W., van Dalen, E.C., Knijnenburg, S.L., van der Pal, H.J., Mud, M.S., Heinen, R.C., Caron, H.N., Kremer, L.C., 2013, "The EKZ/AMC childhood cancer survivor cohort: methodology, clinical charasteristics, and data availability, J Cancer Surviv, vol. 7, no.3, pp. 439-454.

Simony, S.B., Lund, L.W., Erdmann, F., Andersen, K.K., Winther, J.F., Schuz, J., Johansen, C., Schmiegelow, K. & Dalton, S.O. 2016, "Effect of socioeconomic position on survival after childhood cancer in Denmark", Acta Oncologica (Stockholm, Sweden), vol. 55, no. 6, pp. 742-750.

Sisk, C.L. & Foster, D.L. 2004, "The neural basis of puberty and adolescence", Nature neuroscience, vol. 7, no. 10, pp. 1040-1047.

Slater, P.J., Fielden, P.E. & Bradford, N.K. 2017, "The Oncology Family App: Providing Information and Support for Families Caring for Their Child With Cancer", Journal of pediatric oncology nursing : official journal of the Association of Pediatric Oncology Nurses, , pp. 1043454217741874.

Smith, M.A., Altekruse, S.F., Adamson, P.C., Reaman, G.H. & Seibel, N.L. 2014, "Declining childhood and adolescent cancer mortality", Cancer, vol. 120, no. 16, pp. 2497-2506.

Spear, L.P. 2013, "Adolescent neurodevelopment", The Journal of adolescent health : official publication of the Society for Adolescent Medicine, vol. 52, no. 2 Suppl 2, pp. S7-13.

Spiegler, B.J., Kennedy, K., Maze, R., Greenberg, M.L., Weitzman, S., Hitzler, J.K. & Nathan, P.C. 2006, "Comparison of long-term neurocognitive outcomes in young children with acute lymphoblastic leukemia treated with cranial radiation or high-dose or very high-dose intravenous methotrexate", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 24, no. 24, pp. 3858-3864.

Stuber, M.L., Meeske, K.A., Krull, K.R., Leisenring, W., Stratton, K., Kazak, A.E., Huber, M., Zebrack, B., Uijtdehaage, S.H., Mertens, A.C., Robison, L.L. & Zeltzer, L.K. 2010, "Prevalence and predictors of posttraumatic stress disorder in adult survivors of childhood cancer", Pediatrics, vol. 125, no. 5, pp. e1124-34.

Szalda, D., Pierce, L., Hobbie, W., Ginsberg, J.P., Brumley, L., Wasik, M., Li, Y. & Schwartz, L.A. 2016, "Engagement and experience with cancer-related follow-up care among young adult survivors of childhood cancer after transfer to adult care", Journal of cancer survivorship : research and practice, vol. 10, no. 2, pp. 342-350.

Syse, A., Lyngstad, T.H. & Kravdal, O. 2012, "Is mortality after childhood cancer dependent on social or economic resources of parents? A population-based study", International journal of cancer, vol. 130, no. 8, pp. 1870-1878.

Tai, E., Buchanan, N., Townsend, J., Fairley, T., Moore, A. & Richardson, L.C. 2012, "Health status of adolescent and young adult cancer survivors", Cancer, vol. 118, no. 19, pp. 4884-4891.

Taylor, A.J., Croft, A.P., Palace, A.M., Winter, D.L., Reulen, R.C., Stiller, C.A., Stevens, M.C. & Hawkins, M.M. 2009, "Risk of thyroid cancer in survivors of childhood cancer: results from the British Childhood Cancer Survivor Study", International journal of cancer, vol. 125, no. 10, pp. 2400-2405.

Teppo, L., Pukkala, E. & Lehtonen, M. 1994, "Data quality and quality control of a population-based cancer registry. Experience in Finland", Acta Oncologica (Stockholm, Sweden), vol. 33, no. 4, pp. 365-369.

Thalen-Lindstrom, A., Larsson, G., Glimelius, B. & Johansson, B. 2013, "Anxiety and depression in oncology patients; a longitudinal study of a screening, assessment and psychosocial support intervention", Acta Oncologica (Stockholm, Sweden), vol. 52, no. 1, pp. 118-127.

Thariat, J., Hannoun-Levi, J-M., Myint, A., Vuong, T., Gerard, J-P. 2013, "Past, present, and future of radiotherapy for the benefit of patients", Nature Reviews Clinical Oncology, vol. 10, pp. 52-60.

Thompson, J., Coleman, R., Colwell, B., Freeman, J., Greenfield, D., Holmes, K., Mathers, N. & Reed, M. 2013, "Levels of distress in breast cancer survivors approaching discharge from routine hospital follow-up", Psycho-oncology, vol. 22, no. 8, pp. 1866-1871.

Toft, N., Birgens, H., Abrahamsson, J., Griskevicius, L., Hallbook, H., Heyman, M., Klausen, T.W., Jonsson, O.G., Palk, K., Pruunsild, K., Quist-Paulsen, P., Vaitkeviciene, G., Vettenranta, K., Asberg, A., Frandsen, T.L., Marquart, H.V., Madsen, H.O., Noren-Nystrom, U. & Schmiegelow, K. 2017, "Results of NOPHO ALL2008 treatment for patients 1-45 years with acute lymphoblastic leukemia", Leukemia, .

Tonorezos, E.S., Hudson, M.M., Edgar, A.B., Kremer, L.C., Sklar, C.A., Wallace, W.H. & Oeffinger, K.C. 2015, "Screening and management of adverse endocrine outcomes in adult survivors of childhood and adolescent cancer", The lancet.Diabetes & endocrinology, vol. 3, no. 7, pp. 545-555.

Toohey, K., Pumpa, K., McKune, A., Cooke, J. & Semple, S. 2018, "High-intensity exercise interventions in cancer survivors: a systematic review exploring the impact on health outcomes", Journal of cancer research and clinical oncology, vol. 144, no. 1, pp. 1-12.

Turkel, S.B., Tishler, D. & Tavare, C.J. 2007, "Late onset psychosis in survivors of pediatric central nervous system malignancies", The Journal of neuropsychiatry and clinical neurosciences, vol. 19, no. 3, pp. 293-297.

Turner, C.D., Chordas, C.A., Liptak, C.C., Rey-Casserly, C., Delaney, B.L., Ullrich, N.J., Goumnerova, L.C., Scott, R.M., Begley, H.C., Fletcher, W.J., Yao, X., Chi, S. & Kieran, M.W. 2009, "Medical, psychological, cognitive and educational late-effects in pediatric low-grade glioma survivors treated with surgery only", Pediatric blood & cancer, vol. 53, no. 3, pp. 417-423.

Turner, C.D., Rey-Casserly, C., Liptak, C.C. & Chordas, C. 2009, "Late effects of therapy for pediatric brain tumor survivors", Journal of child neurology, vol. 24, no. 11, pp. 1455-1463.

van der Geest, I.M., van Dorp, W., Hop, W.C., Neggers, S.J., de Vries, A.C., Pieters, R., Aarsen, F.K. & van den Heuvel-Eibrink, M.M. 2013, "Emotional distress in 652 Dutch very long-term survivors of childhood cancer, using the hospital anxiety and depression scale (HADS)", Journal of pediatric hematology/oncology, vol. 35, no. 7, pp. 525-529.

van Dijk, I.W., Cardous-Ubbink, M.C., van der Pal, H.J., Heinen, R.C., van Leeuwen, F.E., Oldenburger, F., van Os, R.M., Ronckers, C.M., Schouten-van Meeteren, A.Y., Caron, H.N., Koning, C.C. & Kremer, L.C. 2013, "Dose-effect relationships for adverse events after cranial radiation therapy in long-term childhood cancer survivors", International journal of radiation oncology, biology, physics, vol. 85, no. 3, pp. 768-775.

von der Weid, N., Mosimann, I., Hirt, A., Wacker, P., Nenadov Beck, M., Imbach, P., Caflisch, U., Niggli, F., Feldges, A. & Wagner, H.P. 2003, "Intellectual outcome in children and adolescents with acute lymphoblastic leukaemia treated with chemotherapy alone: age- and sex-related differences", European journal of cancer (Oxford, England : 1990), vol. 39, no. 3, pp. 359-365.

Vuotto, S.C., Krull, K.R., Li, C., Oeffinger, K.C., Green, D.M., Patel, S.K., Srivastava, D., Stovall, M., Ness, K.K., Armstrong, G.T., Robison, L.L. & Brinkman, T.M. 2017, "Impact of chronic disease on emotional distress in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study", Cancer, vol. 123, no. 3, pp. 521-528.

Vyas, A., Babcock, Z. & Kogut, S. 2017, "Impact of depression treatment on health-related quality of life among adults with cancer and depression: a population-level analysis", Journal of cancer survivorship: research and practice, .

Waber, D.P., Queally, J.T., Catania, L., Robaey, P., Romero, I., Adams, H., Alyman, C., Jandet-Brunet, C., Sallan, S.E. & Silverman, L.B. 2012, "Neuropsychological outcomes of standard risk and high risk patients treated for acute lymphoblastic leukemia on Dana-Farber ALL consortium protocol 95-01 at 5 years post-diagnosis", Pediatric blood & cancer, vol. 58, no. 5, pp. 758-765.

Wampler, M.A., Galantino, M.L., Huang, S., Gilchrist, L.S., Marchese, V.G., Morris, G.S., Scalzitti, D.A., Hudson, M.M., Oeffinger, K.C., Stovall, M., Leisenring, W.M., Armstrong, G.T., Robison, L.L. & Ness, K.K. 2012, "Physical activity among adult survivors of childhood lower-extremity sarcoma", Journal of cancer survivorship : research and practice, vol. 6, no. 1, pp. 45-53.

Wenninger, K., Helmes, A., Bengel, J., Lauten, M., Volkel, S. & Niemeyer, C.M. 2013, "Coping in long-term survivors of childhood cancer: relations to psychological distress", Psycho-oncology, vol. 22, no. 4, pp. 854-861.

Wiener, L., Battles, H., Bernstein, D., Long, L., Derdak, J., Mackall, C.L. & Mansky, P.J. 2006, "Persistent psychological distress in long-term survivors of pediatric sarcoma: the experience at a single institution", Psycho-oncology, vol. 15, no. 10, pp. 898-910.

Wiener, L., Oppenheim, D., Breyer, J., Battles, H., Zadeh, S. & Patenaude, A.F. 2012, "A worldview of the professional experiences and training needs of pediatric psycho-oncologists", Psycho-oncology, vol. 21, no. 9, pp. 944-953.

Willard, V.W., Klosky, J.L., Li, C., Srivastava, D.K., Brinkman, T.M., Robison, L.L., Hudson, M.M. & Phipps, S. 2017, "The impact of childhood cancer: Perceptions of adult survivors", Cancer, .

Willems, R.A., Mesters, I., Lechner, L., Kanera, I.M. & Bolman, C.A.W. 2017, "Long-term effectiveness and moderators of a web-based tailored intervention for cancer survivors on social and emotional functioning, depression, and fatigue: randomized controlled trial", Journal of cancer survivorship : research and practice, vol. 11, no. 6, pp. 691-703.

Wittchen, H.U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jonsson, B., Olesen, J., Allgulander, C., Alonso, J., Faravelli, C., Fratiglioni, L., Jennum, P., Lieb, R., Maercker, A., van Os, J., Preisig, M., Salvador-Carulla, L., Simon, R. & Steinhausen, H.C. 2011, "The size and burden of mental disorders and other disorders of the brain in Europe 2010", European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology, vol. 21, no. 9, pp. 655-679.

Wolfe, I., Thompson, M., Gill, P., Tamburlini, G., Blair, M., van den Bruel, A., Ehrich, J., Pettoello-Mantovani, M., Janson, S., Karanikolos, M. & McKee, M. 2013, "Health services for children in western Europe", Lancet (London, England), vol. 381, no. 9873, pp. 1224-1234.

Woodward, E., Jessop, M., Glaser, A. & Stark, D. 2011, "Late effects in survivors of teenage and young adult cancer: does age matter?", Annals of oncology : official journal of the European Society for Medical Oncology, vol. 22, no. 12, pp. 2561-2568.

Zebrack, B.J., Gurney, J.G., Oeffinger, K., Whitton, J., Packer, R.J., Mertens, A., Turk, N., Castleberry, R., Dreyer, Z., Robison, L.L. & Zeltzer, L.K. 2004, "Psychological outcomes in long-term survivors of childhood brain cancer: a report from the childhood cancer survivor study", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 22, no. 6, pp. 999-1006.

Zebrack, B.J., Zeltzer, L.K., Whitton, J., Mertens, A.C., Odom, L., Berkow, R. & Robison, L.L. 2002, "Psychological outcomes in long-term survivors of childhood leukemia, Hodgkin's disease, and non-Hodgkin's lymphoma: a report from the Childhood Cancer Survivor Study", Pediatrics, vol. 110, no. 1 Pt 1, pp. 42-52.

Zebrack, B.J., Zevon, M.A., Turk, N., Nagarajan, R., Whitton, J., Robison, L.L. & Zeltzer, L.K. 2007, "Psychological distress in long-term survivors of solid tumors diagnosed in childhood: a report from the childhood cancer survivor study", Pediatric blood & cancer, vol. 49, no. 1, pp. 47-51.

Zeltzer, L.K., Recklitis, C., Buchbinder, D., Zebrack, B., Casillas, J., Tsao, J.C., Lu, Q. & Krull, K. 2009, "Psychological status in childhood cancer survivors: a report from the Childhood Cancer Survivor Study", Journal of clinical oncology : official journal of the American Society of Clinical Oncology, vol. 27, no. 14, pp. 2396-2404.

Zhang, Y.K., Goddard, J.J., Spinelli, C., Gotay and McBride, M.L.2012,"Risk of Late Mortality and Second Malignant Neoplasms among 5-year Survivors of Young Adult Cancer: A Report of the Childhood, Adolescent, and Young Adult Cancer Survivors Research Program", J Cancer Epidemiol, vol. 2012, 103032.

Zou, P., Li, Y., Conklin, H.M., Mulhern, R.K., Butler, R.W. & Ogg, R.J. 2012, "Evidence of change in brain activity among childhood cancer survivors participating in a cognitive remediation program", Archives of clinical neuropsychology : the official journal of the National Academy of Neuropsychologists, vol. 27, no. 8, pp. 915-929.

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