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LATE MORTALITY AND CARDIOVASCULAR MORBIDITY AFTER CANCER AT A YOUNG AGE IN FINLAND

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To Cancer Survivors

ABSTRACT

Andreina E Kero: **Late Mortality and Cardiovascular Morbidity After Cancer at a Young Age in Finland**

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Advances in cancer therapies have led to an improved survival after childhood cancer, but also to numerous late adverse sequelae. We aimed to analyze late cardiovascular effects, the leading non-malignant complications, and mortality after cancer at a young age.

Via linkage to the hospital discharge registry, we compared cardiovascular complications among 5-year survivors (13,860) younger than 35 years at cancer diagnosis to those of a healthy sibling cohort. Furthermore, the causes of death and purchases of cardiovascular medications and drugs associated with metabolic syndrome were evaluated after early onset cancer and compared to siblings and the general population by accessing the causes-of-death and the drug purchase registers.

Both childhood and young adult cancer survivors were more prone to suffer from all studied cardiovascular conditions than their siblings with the highest hazard ratios (HRs) for cardiomyopathy/ cardiac insufficiency. Standardized mortality ratios (SMRs) were elevated after early onset cancer with respect to overall causes of death, cardiovascular causes, and other causes. Additionally, early onset cancer patients were more likely to purchase drugs for cardiovascular disorders and conditions associated with the metabolic syndrome than siblings. All studied cardiovascular outcomes were highly dependent on the cancer diagnosis and the age at cancer diagnosis.

These studies emphasize the need for setting up long-term cardiovascular follow-up guidelines for early onset cancer survivors, especially in young adult cancer survivors who are still at lack of those. The prevention and early detection of cardiovascular late effects is the ultimate goal for their lifelong medical surveillance to ensure them a best possible quality of life.

Keywords: cardiovascular late effects, childhood and adolescent cancer, drug purchase, registry linkage, young adult cancer.

TIIVISTELMÄ

Andreina E Kero: **Myöhempi kuolleisuus ja sydän- ja verenkiertoelimistön sairaudet nuoruusiän syövän jälkeen Suomessa**

Turun yliopisto, Lääketieteellinen tiedekunta, Kliininen laitos, Lastentautioppi, Turun yliopiston kliininen tohtoriohjelma (TKT); Turun yliopistollinen keskussairaala, Annales Universitaties Turkuensis, Medica-Odontologica, Turku 2017

Kehittyneiden hoitojen myötä suurin osa lapsuudessa ja nuoruusiässä syöpään sairastuneista selviää taudistaan, mutta heille voi ilmaantua muita terveysongelmia syöpähoitojen myöhäisvaikutuksina. Tämän tutkimuksen tavoitteena oli selvittää sydän- ja verenkiertoelimistön sairauksien ilmaantumista ja kuolleisuutta nuoruusiässä syövän sairastaneilla. Hoitoilmoitusrekisterin (HILMO) avulla analysoitiin alle 35-vuotiaana syöpädiagnoosin saaneiden ja syövästä 5 vuotta selviytyneiden (N=13,860) henkilöiden sydän- ja verenkiertoelimistön sairauksia verrattuna sisaruksiin. Lisäksi verrattiin syöpää sairastaneiden kuolinsyitä sekä heidän kardiovaskulaarilääkkeiden ja metabolisen oireyhtymän lääkkeiden ostomääriä sisarusten ja väestön ostomääriin. Nämä tiedot poimittiin kuolinsyyrekisteristä ja KELAn lääkeostorekisteristä.

Lapsuudessa tai nuoruusiässä syöpää sairastaneilla todettiin sisaruksia korkeampi vaara sairastua sydämen ja verenkiertoelimistön sairauksiin. Korkein vaarasuhde koski kardiomyopatiaa/ sydämen vajaatoimintaa. Yli viisi vuotta syövän jälkeen selviytyneiden todettiin menehtyvän ikätovereitaan todennäköisemmin ennenaikaisesti. Syövän lisäksi kuolinsyynä oli verrokkeja useammin sydän- ja verisuonisairaudet. Lisäksi lapsuudessa ja nuoruudessa syövän sairastaneilla todettiin suuremmat vaarasuhteet kardiovaskulaarilääkkeiden ja metabolisen oireyhtymän lääkkeiden ostoihin verrattuna sisaruksiin. Vaarasuhteet tutkimuksen kohteena oleviin sairauksiin olivat selkeästi riippuvaisia syövän diagnoosityypistä ja sairastumisiästä.

Tulokset vahvistavat kansainvälistä käsitystä siitä, että nuorena syövän sairastaneet tarvitsevat systemaattisempaa, yksilöllistä ja monesti elinikäistä myöhäisvaikutusseurantaa. Erityisesti nuorena aikuisena syövän sairastaneille ei ole luotu tarkkoja suosituksia siitä, miten myöhäisvaikutusseuranta on syytä toteuttaa. Optimaalisella pitkäaikaisneuvonnalla sydän- ja verenkiertoelinten sairaudet voitaisiin havaita mahdollisimman varhain ja osa sairastavuudesta pystyttäisiin jopa estämään.

Avainsanat: lasten ja nuorten aikuisten syöpä, lääkitys, myöhäisvaikutukset, sydän- ja verenkiertoelimistön sairaudet, terveydenhuollon rekisterit.

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ABBREVIATIONS

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
ASR	Age-standardized rates
ATC	Anatomical therapeutic chemical
AYA	Adolescents and young adult
CCSS	Childhood Cancer Survivor Study
CD	Cluster of differentiation
CDR	Cause-of-death register
CI	Confidence interval
CNS	Central nervous system
CPG	Clinical practice guideline
DPR	Drug purchase register
FCR	Finnish cancer registry
HDR	Hospital discharge register
HL	Hodgkin's lymphoma
HR	Hazard ratio
HSCT	Hematopoietic stem cell transplantation
ICD-10	International classification of diseases and related health problems, tenth revision
LTFU	Long-term follow-up
metS	Metabolic syndrome
MTX	Methotrexate
NA	Not applicable
NHL	Non-Hodgkin lymphoma
NOPHO	Nordic Society of Pediatric Hematology and Oncology
PIC	Personal identification code
PRC	Population register center
QOL	Quality of life

SMN   Second malignant neoplasm

SMR   Standardized mortality ratio

WHO   World Health Organization

YA   Young adult

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are addressed in the text with the Roman numerals I–IV.

I.   Kero AE, Järvelä LS, Arola M, Malila N, Madanat-Harjuoja LM, Matomäki J, Lähteenmäki PM. Cardiovascular morbidity in long-term survivors of early-onset cancer: a population-based study. Int J Cancer 2014;134:664-73.

II.   Kero AE, Järvela LS, Arola M, Malila N, Madanat-Harjuoja LM, Matomäki J, Lähteenmäki PM. Late mortality among 5-year survivors of early onset cancer: a population-based register study. Int J Cancer 2015;136:1655-64.

III.   Kero AE, Madanat-Harjuoja LM, Järvelä LS, Malila N, Matomäki J, Lähteenmäki PM. Cardiovascular medication after cancer at a young age in Finland: A nationwide registry linkage study. Int J Cancer 2015;139:683-690.

IV.   Kero AE, Madanat-Harjuoja LM, Järvelä LS, Malila N, Matomäki J, Lähteenmäki PM. Health conditions associated with metabolic syndrome after cancer at a young age: A nationwide register-based study. Cancer Epidemiol 2016;41:42-9.

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1   INTRODUCTION

While the incidence of childhood cancer has shown a rising tendency in the USA and Europe, its incidence has remained rather stable in Finland. The increase in incidence may be due to genetic, immunological, or environmental factors. Among the western industrialized countries, the age- standardized incidence rates of childhood cancer in Finland are within the highest ranges concerning patients aged 0-14 years at cancer diagnosis (Kaatsch 2010). The most common childhood cancer diagnosis groups are in descending order: central nervous system (CNS) tumors, acute leukemias, and lymphomas (Figure 1A).

Due to the previous lack of attention, adolescent and young adult (AYA) cancer patients have been referred to as the 'lost tribe' or the 'orphaned population' (Fernandez et al. 2006). The group of young adult (YA) patients with a cancer diagnosis at an age below 39 years has only recently gained appropriate interest (van der Horst et al. 2006, Prasad et al. 2012, Zhang et al. 2012). In the past decades, the incidence of YA cancer has been rising in the USA and also in Finland as a consequence of improved cancer screening and increasing obesity among the population (Bleyer et al. 2006, Barr et al. 2016). After childhood and adolescence, the cancer spectrum shifts to epithelial malignancies, carcinomas, while the incidence of the most frequent pediatric diagnoses, such as ALL and CNS tumors, decreases (Fernandez et al. 2006, Ferreira et al. 2013). The most common YA cancer diagnoses for both sexes combined comprise the following groups: testicular cancer, CNS tumors, thyroid cancer, and breast cancer (Figure 1B). Advances in cancer treatments have led to improved survival rates also after YA cancer, but they still lag behind those of childhood cancer survival for certain types of cancer.

Developments in cancer therapies have led to improved overall 5-year survival rates of around 80% after childhood cancer (Gatta et al. 2014, Madanat-Harjuoja et al. 2014, Trama et al. 2016). The success of curing cancer comes, however, at a high cost in the form of late adverse health effects (Oeffinger et al. 2006, Hudson et al. 2013, Armstrong et al. 2014). It has been shown that two out of three childhood cancer survivors may have chronic health conditions as adults (Oeffinger et al. 2006). Furthermore, at the age of 50 years, every second childhood cancer survivor may be diagnosed with a life-threatening disease (Armstrong et al. 2014). Late adverse conditions may affect any organ system in the form of cardiac, pulmonary, skeletal, urinary tract, gastrointestinal, neurocognitive, auditory, endocrine, and autoimmune diseases (Oeffinger et al. 2006, Hudson et al. 2013, Gunn et al. 2015 A, Holmqvist et al. 2015).

Cardiovascular late effects are the leading non-malignant causes of death in childhood and young adult cancer survivors (Mertens et al. 2001, Moller et al. 2001, Mertens et al. 2008, Reulen et al. 2010, Garwicz et al. 2012, Prasad et al. 2012, Zhang et al. 2012, Armstrong et al. 2016). After childhood cancer, the risk for cardiovascular complications, such as congestive heart failure, pericardial disease, myocardial infarction, and valvular disorders, is markedly increased compared to siblings

(Mulrooney et al. 2009). Exposure to anthracyclines and mediastinal irradiation significantly increases the risk for cardiac adverse effects (van Dalen et al. 2006, Mulrooney et al. 2009). Other chemotherapeutic drugs, such as alkylating agents, especially busulfan, and the antitumor antibiotic mitomycin, are also associated with cardiac damage (Simbre et al. 2005). While the underlying causes of cardiotoxicity remain to be unraveled, myocyte apoptosis and myocardial fibrosis may be involved (Lipshultz et al. 2013 A).

Mortality after childhood and young adult cancer is higher than among healthy controls (Mertens et al. 2001, Moller et al. 2001, Mertens et al. 2008, Reulen et al. 2010, Garwicz et al. 2012, Prasad et al. 2012, Zhang et al. 2012, Armstrong et al. 2016). While secondary malignant neoplasms impose the greatest lethal threat in the first years after cancer diagnosis, cardiovascular diseases are the dominating non-malignant cause of death with a growing incidence over time (Mertens et al. 2008, Reulen et al. 2010, Garwicz et al. 2012, Prasad et al. 2012, Zhang et al. 2012).

The data for studies on the late effects after childhood cancer origin from many sources: medical examinations, laboratory tests, questionnaires, and registry information (Oeffinger et al. 2006, Hudson et al. 2013, Armstrong et al. 2016). However, numerous articles, being institution-based or based on medical check-ups, have analyzed rather small numbers of childhood cancer survivors (Kremer et al. 2001, Geenen et al. 2007, Lipshultz et al. 2012). While the largest studies have been based on questionnaires (CCSS) or registry data of childhood cancer survivors (Oeffinger et al. 2006, Hudson et al. 2013, Armstrong et al. 2016), reports on large cohorts after young adult cancer are still rare (Garwicz et al. 2012, Prasad et al. 2012). There are only few studies on very late adverse effects after cancer treatment at a young age (Garwicz et al. 2012, Armstrong et al. 2014).

The analysis and prevention of late effects after childhood cancer are gaining interest among scientists (Oeffinger et al. 2006, Hudson et al. 2013, Armstrong et al. 2014). In contrast to the numerous reports on childhood cancer survivors, studies after young adult cancer are rather scarce and have only recently generated interest (Prasad et al. 2012, Zhang et al. 2012, Trama et al. 2016). Analogously to childhood cancer, young adult (YA) cancer predisposes to chronic health conditions and premature mortality. In addition to cancer therapy, there are modifiable cardiovascular risk factors after childhood cancer which add to the excess risk for premature death and cardiovascular illness (Armstrong et al. 2013). Thus, a healthy life-style and regular physical activity are important, especially after early onset cancer to reduce and possibly prevent late cardiovascular complications.

This thesis addressed the long-term adverse cardiovascular sequelae of patients who had been treated for cancer at an early age (younger than 35 years at cancer diagnosis). The research method was a linkage of nationwide, population-based registries. While late complications have extensively been studied after childhood cancer, there is a paucity of research data on late complications after YA cancer. The studies of this thesis offer

novel, important insights on the cardiovascular late sequelae and mortality after both childhood and YA cancer compared to siblings and the general population. Additionally, this thesis describes the purchase of cardiovascular drugs and medications associated with the metabolic syndrome after cancer at an early age to demonstrate cardiovascular conditions also on an out-patient basis. This information may contribute to the development of individualized risk-based long-term surveillance after cancer at a young age. Appropriate long-term follow-up may prevent and reduce the potentially lethal impact of cardiovascular late effects in this growing population at risk for premature cardiovascular death. Thus, the implementation of cardiovascular follow-up guidelines is pivotal to offer cancer survivors the best possible quality of life.
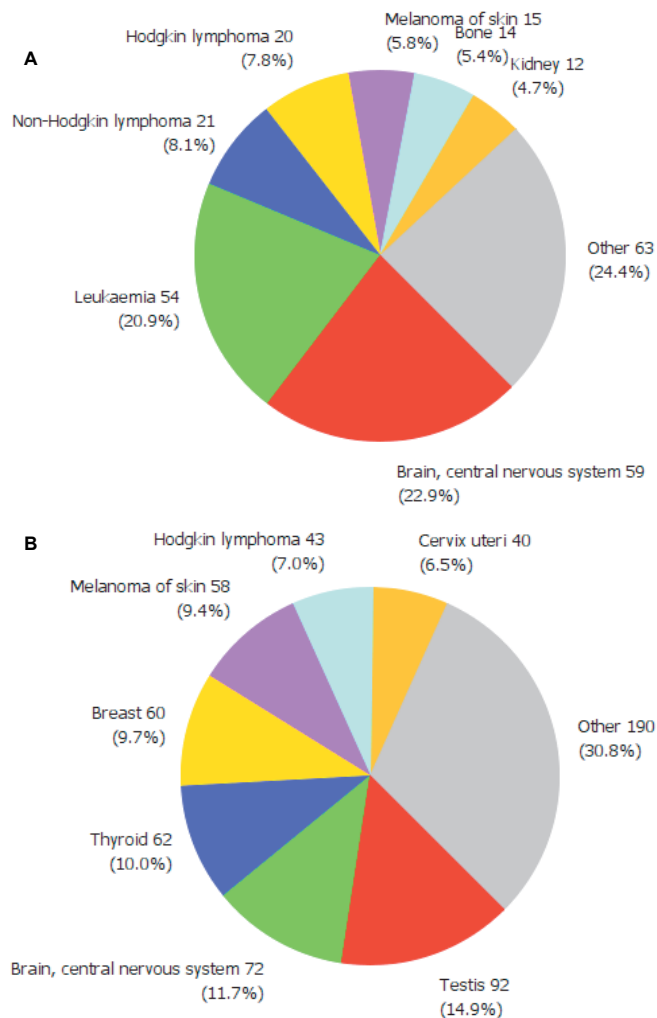
Figure 1: Numbers and percentages describing the incidence of cancer diagnoses in Finland (2014): A) childhood cancer (younger than 20 years at cancer diagnosis) and B) young adult cancer (aged 20 and 34 years at cancer diagnosis). Published with the permission of NORDCAN (Engholm et al. 2010).

2   REVIEW OF THE LITERATURE

2.1   EARLY ONSET CANCER: SURVIVAL

2.1.1 Survival after cancer in childhood

Numerous studies and therapy trials show that the overall 5-year survival rates after childhood cancer are about 80% for all cancer diagnoses taken together (Magnani et al. 2006, Kaatsch 2010, Gatta et al. 2014, Smith et al. 2010) (Table 1A). Furthermore, 5-year survival rates surpassing 90% have been reported in certain standard-risk childhood cancers, e.g., acute lymphoblastic leukemia (ALL) and Hodgkin's lymphoma (HL) (Kaatsch et al.2010, Smith et al. 2010, Gatta et al. 2014) (Table 1A). In Finland, the current survival rates after childhood cancer are among the highest in the world (Gatta et al. 2014, Madanat-Harjuoja et al. 2014) (Table 1A). The 5-year survival rates after childhood malignant bone tumors and childhood acute myeloid leukemia are much lower, leaving many opportunities for advances in cancer therapies. (Table 1A). While the outcomes of many childhood cancer treatments have greatly improved during the last decades, there is room for improvement in areas of high-risk diagnoses and rare cancer types. Advances in these challenging subgroups of childhood cancer diagnoses may be made by forming international collaborative groups to plan and run additional trials (Gatta et al. 2014).

2.1.2 Survival after cancer in young adulthood

While the overall 5-year survival rate in AYA survivors aged 15 to 39 years at cancer diagnosis is around 79%, many survival outcomes still lag behind that of the corresponding childhood cancers (Trama et al. 2016). Decisive advances in cancer therapy have been reached for ALL and HL, and 5-year survival rates approach 75% and 93.9%, respectively (Table 1B). Concerning the treatment of YA ALL, a more aggressive therapeutic approach, including treatment elements from the pediatric ALL treatment protocols, have led to decisive advances in outcome despite a slightly increased toxicity in the older cancer patients (Huguet et al. 2009, Toft et al. 2013, Hough et al. 2016, Toft et al. 2016). The 5-year overall survival rates of nearly 100% after YA thyroid cancer contrast to the corresponding rates of merely 47% after YA acute myeloid leukemia (AML) (Table 1B). The question of where the best available cancer treatment for specific diagnoses should be managed is unresolved, since the optimum cut-off age at cancer diagnosis for referral to either a pediatric or an adult oncological treatment center is contentious (Marris et al. 2011, Trama et al. 2016). Lower survival rates for certain cancer diagnoses could also be partially explained by a markedly lower number of YA cancer trials and a lower compliance of YA cancer patients compared to experiences from childhood cancer treatments (Bleyer et al. 2006, Ferrari et al.2008).

Table 1A: 5-year overall survival after childhood cancer by diagnosis, age at diagnosis, time period of cancer diagnosis, and cohort. ALL= acute lymphoblastic leukemia. AML= acute myeloid leukemia, HL= Hodgkin's lymphoma, NHL= non-Hodgkin lymphoma, CNS= central nervous system tumors, Osteosarc= osteosarcoma, Ewing/ other= other sarcomas of the bone (except osteosarcomas), y= year, na= not available.[1] (Gatta et al. 2014), [2] (NOPHO Annual Report 2016), [3] (Madanat-Harjuoja et al. 2014).

Cohort	Diagnosis	Cohort size	Age at diagnosis	Diagnosis period	5-year survival	95% CI
Europe[1]	All diagnoses	157,499	<15y	2000-2007	77.9%	77.4-78.3
	ALL	15,860	<15y	2000-2007	86.3%	85.5-87.1
	AML	3,094	<15y	2000-2007	62.7%	60.5-64.9
	HL	3,142	<15y	2000-2007	95.4%	94.1-96.5
	NHL	2,544	<15y	2000-2007	84.0%	82.0-85.8
	CNS	9,277	<15y	2000-2007	57.5%	56.0-58.8
	Osteosarc	1,500	<15y	2000-2007	69.3%	66.2-72.3
	Ewing/other	1,397	<15y	2000-2007	67.9%	64.2-71.2
	ALL	1,378	15-19y	2000-2007	62.2%	60.6-63.8
	AML	704	15-19y	2000-2007	52.2%	50.0-54.4
	HL	3,541	15-19y	2000-2007	94.3%	93.8-94.8
	NHL	1,217	15-19y	2000-2007	78.0%	76.6-79.4
	CNS	1,464	15-19y	2000-2007	61.8%	60.3-63.3
	Osteosarc	765	15-19y	2000-2007	60.3%	58.1-62.5
	Ewing/other	448	15-19y	2000-2007	51.1%	47.4-53.8
Nordic[2]	ALL	1,449	1-17y	2008-2014	93.0%	92.0-94.0
	AML	323	<15y	2004-2014	69.0%	na
	HL	700	<15y	1985-2014	96.0%	95.0-97.0
	NHL	899	<15y	1985-2014	82.0%	81.0-83.0
	NHL Burkitt	311	<15	1985-2014	89.0%	87.0-91.0
	CNS	5,922	<15 y	1985-2014	77.0%	76.0-80.0
	Bone	821	<15y	1985-2014	70.0%	68.0-72.0
Finland[3]	All diagnoses	8,270	<15y	2001-2010	82.1%	80.0-84.2
	ALL	404	<15y	2001-2010	86.3%	79.4-88.0
	AML	59	<15y	2001-2010	70.7%	49.5-84.3
	HL	51	<15y	2001-2010	97.2%	78.8-99.7
	NHL	84	<15y	2001-2010	88.7%	74.5-95.2
	CNS	358	<15y	2001-2010	79.1%	70.1-85.7
	Bone	34	<15y	2001-2010	71.3%	45.0-86.6

Table 1B: 5-year overall survival after young adult cancer by diagnosis, age at diagnosis, time period of cancer diagnosis, and cohort. ALL= acute lymphoblastic leukemia, AML= acute myeloid leukemia, HL= Hodgkin's lymphoma, NHL= non-Hodgkin lymphoma, CNS= central nervous system tumors, Germ cell gonadal= malignant gonadal germ cell tumors, ca= cancer, Male genital tract= carcinomas including testicular, penile and prostate carcinoma, Female genital tract= carcinomas comprising ovarian and uterine tumors, y= year, na= not available. [1] (Trama et al. 2016), [2] (NOPHO Annual Report 2016), [3] (Toft et al. 2016), [4] (Anders et al. 2009).

Cohort	Diagnosis	Cohort size	Age at diagnosis	Diagnosis period	5-year survival	95% CI
Europe[1]	ALL	3,239	20-39y	2000-2007	52.8%	51.8-53.8
	ALL	797	20-24y	2000-2007	45.6%	43.6-47.6
	ALL	585	25-29y	2000-2007	47.8%	45.4-50.2
	ALL	1,104	30-34y	2000-2007	53.6%	51.5-55.7
	AML	4,484	20-39y	2000-2007	49.4%	48.5-50.3
	AML	819	20-24y	2000-2007	55.2%	53.1-57.3
	AML	1,018	25-29y	2000-2007	47.7%	45.9-49.5
	AML	1,104	30-34y	2000-2007	49.3%	47.6-51.0
	HL	15,735	20-39y	2000-2007	92.6%	92.3-92.9
	HL	4,457	20-24y	2000-2007	93.9%	93.5-94.3
	HL	4,164	25-29y	2000-2007	93.9%	93.4-94.4
	HL	3,816	30-34y	2000-2007	91.6%	91.0-92.2
	NHL	13,840	20-39y	2000-2007	77.3%	76.9-77.7
	CNS	12,722	20-39y	2000-2007	56.1%	55.6-56.6
	Germ cell gonadal	821	20-39y	2000-2007	94.9%	94.7-95.1
	Melanoma	34,994	20-39y	2000-2007	88.9%	88.6-89.2
	Thyroid ca	19,396	15-39y	2000-2007	99.2%	99.1-99.3
	Breast ca	52,468	15-39y	2000-2007	83.5%	81.5-85.5
	Female genital tract	31,460	15-39y	2000-2007	81.6%	81.3-81.9
	Male genital tract	811	15-39y	2000-2007	80.1%	78.2-81.9
Nordic[2]	ALL	250	18-45y	2008-2014	75.0%	72.0-78.0
Nordic randomized[3]	ALL	221	18-45y	2008-2014	73.0%	70.0-76.0
USA[4]	Breast ca	531	20-24y	2000-2005	75.0%	na
	Breast ca	3,397	25-29y	2000-2005	72.0%	na
	Breast ca	11,173	30-34y	2000-2005	76.0%	na

2.2 LATE ADVERSE EFFECTS AFTER EARLY ONSET CANCER

As the survival rates for childhood and YA cancer have improved during the recent decades, there is a growing survivor population at an increased risk for morbidity and mortality compared to the general population (Mertens et al. 2001, Moller et al. 2001, Oeffinger et al. 2006, Mertens et al. 2008, Reulen et al. 2010, Garwicz et al. 2012, Prasad et al. 2012, Zhang et al. 2012 Hudson et al. 2013, Armstrong et al. 2016). These cancer survivors are at a great need for lifelong follow-up to detect or even prevent morbidities. This, in turn, could reduce the excess mortality rates and improve the quality of life of long-term cancer survivors.

2.2.1 Overview of late adverse effects

It is crucial to collect new long-term follow-up data from large patient populations. Moreover, it is pivotal to obtain information on early onset cancer survivors who have been treated most recently to draw conclusions on the effects of cancer therapy. The knowledge on late sequelae may help to improve and modify cancer treatments and the risk-based surveillance during and after cancer therapy. This has been successfully achieved in several large childhood and a few young adult cancer studies. While second malignant neoplasms (SMNs) after childhood cancer have been extensively studied and recognized as leading complications, further interest has arisen in the non-malignant consequences of cancer and cancer therapy (Neglia et al. 2001, Hudson et al. 2013) (Figure 2).
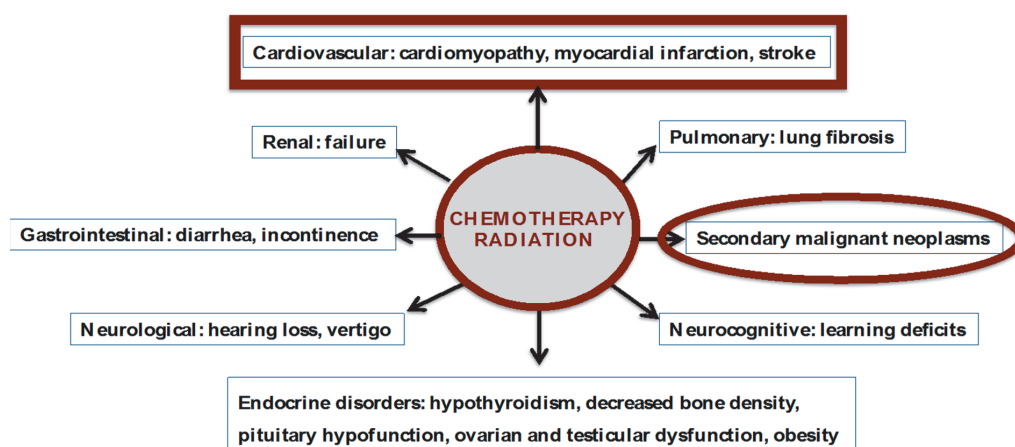
Figure 2: Overview of the late adverse health effects of cancer therapy. Second malignant neoplasms are the greatest lethal threat, followed by cardiovascular late complications as the primary non-malignant cause of death. Virtually any organ system may be damaged.

Prior studies have focused on the long-term adverse effects after childhood cancer to determine the morbidities in this cancer survivor population (Table 2). Information on health outcomes has been assessed via questionnaires (Mertens et al. 2002, Hudson et

al. 2003, Oeffinger et al. 2006) and medical data has been retrieved via registries or medical check-ups (Geenen et al. 2007, Hudson et al. 2013) (Table 2). The large North American childhood cancer survivor study (CCSS) reported that two out of three cancer survivors have at least one chronic health condition and up to 25% have some severe health condition. These figure underline the high proportion of morbidity in the cancer survivor population (Oeffinger et al. 2006). While only 3.3% of siblings reported severe health at the age of 20 years, 1 in 6 childhood cancer survivors had severe medical conditions as 20-year-olds (Armstrong et al. 2014). This difference in deteriorated health status persisted over time among cancer survivors: By the age of 50 years, every second childhood cancer survivor versus 1 out of 5 siblings developed a life-threatening complication (Armstrong et al. 2014).

The variety of described late effects after childhood cancer is manifold. Virtually any organ system is affected, ranging from cardiovascular, pulmonary, endocrine, auditory, skeletal, hepatic, autoimmune, and renal disease to neurocognitive dysfunction (Geenen et al. 2007, Madanat et al. 2008 A, Hudson et al. 2013, Holmqvist et al. 2015) (Figure 2). Among all childhood cancer diagnoses, brain and bone tumor survivors experienced life-threatening health events at the highest extent (Hudson et al. 2003, Oeffinger et al. 2006, Geenen et al. 2007). This high morbidity level was associated with specific cancers and their treatments, including radiation therapy and certain chemotherapeutic agents, e.g., anthracyclines.

Concerning the treatment-related effects, the highest risk for severe health events occurred after radiation therapy, rather than after chemotherapy or surgery only according to a Dutch childhood cancer study (Geenen et al. 2007). Radiotherapy was associated with cardiovascular, endocrine, neurologic, psychosocial, and neurocognitive complications, in addition to second malignancies, an observation which had been reported previously (Gurney et al. 2003, Mulhern et al. 2005, Geenen et al. 2007). The combination of mediastinal irradiation with either bleomycin, anthracyclines, or pelvic and abdominal irradiation could lead to a tenfold increased risk for a life-threatening outcome compared with healthy siblings (Oeffinger et al. 2006, Geenen et al. 2007). The negative health effects of chemotherapy include cardiovascular, pulmonary, fertility, and renal disorders.

Table 2: Characteristics of the largest childhood and young adult cancer cohorts worldwide. This overview shows major differences in study design, the time period of the cancer diagnosis, the age ranges at cancer diagnosis, and the follow-up time.

Study	Study design	Cancer diagnosis	Age at diagnosis	End of follow-up	Cohort size	Reference group	Outcome assessment
CCSS (Mulrooney et al. 2009) Childhood Cancer Survival Study	Multicenter retrospective cohort	1970–1986	<21 years	1.11.2000	20,720	Siblings	Medical evaluation/ records, questionnaires
EKZ/ AMC (Geenen et al. 2010) Emma Children's Hospital Academic Medical Center (Amsterdam, Holland)	Single-center retrospective, and prospective screening	1966–2002	<18 years	31.12.2008	1,822	n.a.	Comprehensive questionnaires
BCCSS (Reulen et al. 2010) British Canadian Childhood Cancer Study	Population-based retrospective cohort	1940–1991	<15 years	17.9.2006	17,866	n.m.	Comprehensive questionnaires
CAYACS (Zhang et al. 2012) Childhood, adolescent and young adult cancer survivors (British Columbia, Canada)	Population-based retrospective cohort	1970–1995	<25 years	31.12.2000	3,841	Matched, general population	Registry-linkage
SJLIFE (Hudson et al. 2013) St Jude for Life Memphis, Tennessee, USA	Single-center retrospective, and prospective screening	1962–2001	<21 years	1.1.2010	3,900	n.a.	Medical evaluation, questionnaires
SCCSS (Gianinazzi et al. 2014) Swiss childhood cancer survival study	Population-based retrospective cohort	1976–2010	<15 years	31.12.2011	5,553	General population siblings	Registry-linkage, medical evaluation, questionnaires
NCCC (Garwicz et al. 2012) Nordic Countries Childhood Cancer Cohort	Population-based retrospective cohort	1960–199	<20 years	31.12.2005/6	37,515	General population	Registry-linkage
ALiCCS (Holmqvist et al. 2014) Adult Life after Childhood Cancer in Scandinavia (Nordic countries)	Population-based Retrospective cohort	1943,1953/5 /8–2008	<20years	2008/2010	43,909	General population	Registry-linkage
GCCR (Petersen et al. 2013) German Childhood Cancer Register	Multi-center institution-based cohort	1980–2009	<15 years <18y after 2009	2010	46,115	General population	Questionnaires, registry data
FCRC (Madanat-Harjuoja et al. 2010) Finnish Cancer Register Cohort	Population-based retrospective cohort	1966–1999	<34years	31.12.2011	9,245	General population, siblings	Registry-linkage, medical records

2.2.2 *Endocrinological complications*

Up to 62% of childhood cancer survivors suffer from late endocrinological complications (Gleeson et al. 2001, Sklar et al. 2001, Hudson et al. 2013, de Fine Licht et al. 2014). Radiation therapy and hematopoietic stem cell transplantation (HSCT) present a stronger risk factor for several endocrinological disorders than chemotherapy (Chemaitilly et al. 2007, Nandagopal et al. 2008). Since HSCT is often carried out as a combination of chemotherapy and total body irradiation, numerous endocrinological negative consequences are possible: growth hormone (GH), corticotropin, thyrotropin, and gonadotropin deficiency, therapy-induced hypothyroidism, autoimmune thyroid disease, thyroid neoplasms, disturbances in fertility, bone density, growth, and glucose homeostasis (Taskinen et al. 2000, Chemaitilly et al. 2007, Niinimaki et al. 2014).

The patient's age at the time of treatment may be crucial for the risk for certain late complications (Lipshultz et al. 1995). Earlier age at HSCT is a risk factor for growth deficiencies, while fertility problems occurred preferentially after HSCT in puberty. In general, late effects following HSCT are more likely to become manifest in patients treated in childhood or adolescence than at older age (Chemaitilly et al. 2007). Fractioned rather than one-time irradiation also reduces the mentioned sequelae substantially.

Among the cancer treatment alternatives, cranial irradiation stands out as a risk for endocrinological late complications in comparison to total body irradiation. Cranial irradiation may cause central adrenal insufficiency, precocious puberty, obesity, and hyperlipidemia (Nandagopal et al. 2008). As after HSCT, the degree of endocrinological complications depends on the irradiation field, the radiation dose, and the patient's age at treatment (Nandagopal et al. 2008). Cranial irradiation is associated with the occurrence of hypothyroidism. In childhood cancer survivors below 15 years at diagnosis, hypothyroidism depends strongly on the type of cancer and its treatment. HL, CNS, and thyroid cancer survivors had the highest rates of hypothyroidism, because the irradiation field may inadvertently reach the thyroid during radiotherapy (Madanat et al. 2008).

Although there is a smaller range of adverse endocrinological effects after chemotherapy compared to irradiation, screening for endocrinological disorders after cancer treatment in general is recommended as part of follow-up, particularly concerning gonadal dysfunction and disturbances of the lipid and bone metabolism. Early onset cancer survivors had fewer offspring than their siblings regardless of gender (Madanat et al. 2008).

2.2.3 *Neurocognitive and psychological consequences*

Neurocognitive impairment is a frequent late complication among childhood cancer survivors. Almost 50% of childhood cancer survivors in a study on a variety of cancers had neurocognitive impairment (Nandagopal et al. 2008). Particularly cranial irradiation placed childhood cancer survivors at a high risk for neurocognitive sequelae. As a

consequence, especially brain tumor survivors were at a greater risk for neurocognitive and psychological dysfunctions compared to other survivors (Ellenberg et al. 2009, Gunn et al. 2015 B). The highest risks for these outcomes were associated with the site of irradiation (partial versus whole brain), the radiation type, female sex, and a younger age at treatment (Kadan-Lottick et al. 2010).

Neurocognitive and psychological deficits may present as memory, attention, processing speed, and behavioral problems. In addition to CNS tumor patients, childhood ALL and AML survivors that have received radiation therapy are subject to neurocognitive defects (Kadan-Lottick et al. 2010). A total cranial irradiation dose above 18 Gray raises the risk for early onset cognitive and memory deficits among childhood ALL and other non-CNS malignancy survivors (Moricke et al. 2008, Kadan-Lottick et al. 2010).

Apart from irradiation, certain chemotherapeutic drugs, such as methotrexate (MTX) (crosses the blood-brain barrier), corticosteroids, anthracyclines, alkylating agents (cyclophosphamide), antimetabolites (fluorouracil), and intrathecal chemotherapy (with MTX) may contribute to a neurocognitive damage (Wefel et al. 2008). Intense CNS-centered therapy with MTX in childhood ALL patients has led to lower neurocognitive functions compared to lower intrathecal exposure to MTX (Duffner et al. 2014). Cranial irradiation and chemotherapy below an age of 7 years in females is associated with poor school performance according to a Finnish investigation on childhood leukemia patients (Harila-Saari et al. 2007). Furthermore, childhood NHL patients obtain lower academic scores than controls after CNS-directed chemotherapy, in line with the childhood ALL study (Lahteenmaki et al. 2008). The knowledge on the adverse consequences of brain irradiation have led to a reduction of this form of cancer therapy without comprising the outcome of cancer therapy for treating certain childhood cancer diagnoses, such as ALL and brain tumors (Rutkowski et al. 2005, Lahteenmaki et al. 2007, Moricke et al. 2008).

With respect to the quality of life (QOL) and the mental status after childhood cancer, data is inconclusive. Comparisons between studies are difficult due to differing sample sizes, diagnoses, reference groups, choice of particular psychological outcomes, and study methods (Mackie et al. 2000, Schwartz et al. 2006, Zebrack et al. 2007, Stuber et al. 2010, Mort et al. 2011 A, Gunn et al. 2015 C). Similarly, inhomogeneous study designs and study questions hamper the interpretations of reports on the psychological burden after young adult cancer (Sansom-Daly et al. 2013). Among childhood cancer survivors, lower health-related scores for the QOL have been reported after osteosarcoma, Wilms' tumor, and neuroblastoma and after treatment with HSCT (Mort et al. 2011 B). Posttraumatic stress disorder (PTSD) is more common among childhood cancer survivors compared to their siblings (Stuber et al. 2010). Even after aggressive anticancer therapy and possible late adverse effects, childhood cancer survivors may still develop a positive state of mind and outlook on their lives after coping with the past (Parry et al. 2005).

In general, risk factors for negative psychological consequences after YA cancer are: female gender, solid tumors or CNS tumors, and the time-point of examinations (before, during, or after treatment) (Sansom-Daly et al. 2013). A study on the health-related quality of life (HRQL) of YA cancer survivors aged 18 to 39 years at diagnosis revealed a poorer physical and emotional status compared to healthy controls (Salsman et al. 2014). Surprisingly, scores are higher for social well-being in YA cancer survivors compared to controls (Salsman et al. 2014). Positive psychological outcomes after YA cancer have been a neglected area of research, but post-traumatic growth (PTG) does take place in YA cancer survivors compared to controls (Sansom-Daly et al. 2013), which is in agreement with findings from childhood cancer survivors (Parry et al. 2005).

2.2.4 *Cardiovascular, cerebrovascular, and pulmonary late effects*

Cardiovascular late outcomes after childhood and YA cancer therapy have been recognized as one of the most serious non-malignant complications (Kremer et al. 2001, Oeffinger et al. 2006, van den Belt-Dusebout et al. 2006, Mertens et al. 2008, van der Pal et al. 2012, Prasad et al. 2012, Chao et al. 2016). This underlines the lethal risk for this category of morbidity among a growing group of cancer survivors. With respect to pulmonary complications, childhood and YA cancer survivors are at an increased risk for recurrent pneumonia, pulmonary fibrosis, and emphysema compared to their healthy siblings (Mertens et al. 2002, Prasad et al. 2012). Childhood and YA cancer survivors are also more prone develop valvular heart disease and hypertension than their siblings (Kenney et al. 2010, Rugbjerg et al. 2014). Furthermore, the prevalence of other cardiac outcomes, such as congestive heart failure, myocardial infarction, pericardial disease, and valvular abnormalities is much higher in childhood cancer survivors than their siblings. The most striking difference is reportedly congestive heart failure (Mulrooney et al. 2009, Rugbjerg et al. 2014), but the total number of cases has been low ,since the overall occurrence of congestive heart failure in this patient population is small. Subclinical cardiotoxicity has been defined as an increased afterload or systolic dysfunction in echocardiography or radionuclide angiocardiography (Kremer et al. 2002 A).

While most studies have focused on symptomatic cardiovascular complications, the assessment of asymptomatic cardiovascular adverse effects is important with respect to the prevention and the reduction of this health burden to the cancer survivor (Kremer et al. 2002 A, Sieswerda et al. 2012).The incidence of subclinical cardiotoxicity has ranged from 0% to 57% among childhood cancer survivors in previous studies (Kremer et al. 2002 A). The wide range of these findings is due to differing diagnosis cohorts and, possibly, biased echocardiographic measurements. Nevertheless, these results demonstrate the imposing threat of unrecognized cardiovascular late effects after successful cancer therapy. Further well known risk factors for late cardiac conditions include female gender, mediastinal irradiation, and a younger age at cancer diagnosis (Lipshultz et al. 1995, Aleman et al. 2007, Mulrooney et al. 2009, van der Pal et al. 2010).

The incidence of cardiac outcomes in the study by Mulrooney et al. was 1.7% among cancer survivors compared to only 0.5% of the sibling cohort (Mulrooney et al. 2009). While the cumulative incidences for congestive heart failure, valvular abnormalities, and pericardial disease kept rising with increasing time from cancer diagnosis, the incidence of myocardial infarction may reach a plateau (Mulrooney et al. 2009). The hazard ratios (HRs) for cardiac late effects were higher among all cancer patients compared to siblings. The HRs were reported for HL (HR 6.8, 95% CI 3.9-11.7) and bone cancer survivors (HR 6.5, 95% CI 3.6-12.0) for congestive heart failure, which underlines the negative consequence of the exposure to anthracyclines. The diagnosis of neuroblastoma is associated with one of the highest HR for myocardial infarction (HR 11.1, 95% 3.3-36.9). In general, childhood and YA HL survivors have been associated with the highest HRs for cardiovascular outcomes compared to other diagnosis groups. The childhood and YA HL survivors' high treatment-related risk for cardiac complications is associated with the combination of mediastinal irradiation and the exposure to anthracyclines during cancer treatment (Mulrooney et al. 2009, Rugbjerg et al. 2014). Since the therapy for HL often includes radiation therapy in addition to anthracycline administration, HL survivors are at increased risk for late adverse cardiovascular complications (Hull et al. 2003). Among HL survivors aged up to 40 years at diagnosis, particularly the age below 20 years at diagnosis is associated with a high risk for myocardial infarction, angina pectoris, and congestive heart failure (Aleman et al. 2007).

In addition to childhood and YA HL, survivors of childhood and YA bone cancer, acute leukemias, and neuroblastoma were reported to most likely sustain cardiac complications (Mulrooney et al. 2009). The risk for anthracycline-induced clinical heart failure in childhood cancer survivors rises with increasing time since the first anthracycline dose from 2% after 2 years to 5.5% after 20 years (Kremer et al. 2001, van der Pal et al. 2012). The increased awareness of the cardiotoxic effects of anthracyclines has led to reductions in the cumulative dose and to intensified cardiac surveillance during the administration of anthracyclines. Congestive heart failure, cardiac arrhythmia, valvular heart disease, and myocardial infarction/ ischemia are the prevailing adverse cardiac complications after childhood cancer (van der Pal et al. 2012). Among the treatment-related effects, the combination of mediastinal irradiation and the exposure to anthracyclines is associated with the highest risk for cardiac complications later in life (Aleman et al. 2007, van der Pal et al. 2012).

There has been a paucity of studies on cardiovascular late effects after YA cancer. Up to date, reports focusing on cardiovascular late effects from adult cancer populations have often included the YA cancer patient group (Hull et al. 2003). Furthermore, studies assessing cardiovascular complications have included only certain YA diagnosis groups, such as testicular cancer and Hodgkin's lymphoma and only few reports exist on a heterogeneous YA cancer population (Hull et al. 2003, van den Belt-Dusebout et al. 2006, Aleman et al. 2007, Chao et al. 2016, Rugbjerg et al. 2014). While the risk for valvular disease is highest after YA HL and leukemia, breast cancer survivors are the

most likely patient group to develop cardiomyopathy and cerebral hemorrhage (Rugbjerg et al. 2014, Chao et al. 2016).

In addition to the direct effects on the myocardium, cerebrovascular complications such as stroke occur also in childhood cancer survivors. The risk for stroke is increased in survivors of childhood and YA leukemia, HL, and CNS tumor (Hull et al. 2003, Bowers et al. 2005, Bowers et al. 2006). In YA and adulthood cancer, stroke is associated with irradiation to the neck which may promote atherosclerosis (Hull et al. 2003). Analogously, mantle irradiation also increases the risk for stroke in childhood and adolescent cancer survivors, as does cranial radiation therapy (Gurney et al. 2003, Bowers et al. 2005). A recent study of childhood CNS tumor survivors confirmed some additional risk factors for stroke: hypertension, cranial radiation therapy, and diabetes mellitus (Mueller et al. 2013).

2.3   EXCESS MORTALITY AFTER EARLY ONSET CANCER

2.3.1 *Mortality of childhood cancer survivors*

The improved survival rates after early onset cancer due to advances in therapy are overshadowed by the long-term morbidity and excess mortality following cancer treatment (Reulen et al. 2010). Before 1970, surgery and radiation were the cornerstones of cancer treatment, which changed with the advent of chemotherapy (Robertson et al. 1994, Armstrong et al. 2009, Armstrong et al. 2016). The 5-year survival is as a benchmark for cancer cure after successful treatment and it has been defined as a minimum survival time for a patient to be considered a cancer survivor. The 5-year survival is a common inclusion criterion of subjects in studies on mortality, but also on morbidity (Trama et al. 2016).

A large observation study of childhood cancer survivors in the USA (up to 30 years from diagnosis) found that the all-cause age-adjusted mortality rates of cancer survivors exceed significantly those of the general population (Armstrong et al. 2009, Armstrong et al. 2016). The overall cumulative mortality rose over time from 6.5% at 10 years to 18.1% at 30 years from diagnosis. Hence, the long-term follow-up of childhood cancer survivors is necessary for the early detection and treatment of morbidity to reduce the excess mortality of childhood cancer survivors. The primary cause of death, especially in the first years from diagnosis, is recurrence or progression of the primary malignant disease. After 15 years from diagnosis, there is a shift from malignancy recurrence or progression as the primary cause of death to non-malignant causes (Robertson et al. 1994, Armstrong et al. 2009). The cancer-related mortality rates of childhood cancer patients seemed to be highest between 5 and 9 years from cancer diagnosis (Standardized mortality ratio (SMR) 20.7, 95% CI 19.6-21.8) with a declining tendency up to 34 years from diagnosis (SMR 6.9, 95%CI 4.7-9.8). Additionally, a younger age than 4 years at diagnosis was associated with the highest SMRs. Certain diagnosis

groups are at a higher risk for all-cause mortality, as also observed previously with respect to morbidities. CNS tumors carried the greatest risks of death (SMR 12.9, 95% CI 11.8-14.0) with medulloblastoma and PNET survivors showing the highest SMR figures. Childhood acute leukemia, Ewing's sarcoma and HL survivors had also increased all-cause mortality figures compared with the general population (Armstrong et al. 2009).

The following causes of death are the most common after childhood cancer in comparison to the general population: secondary malignancies, pulmonary events, and cardiac events. Female gender is associated with higher mortality ratios across all causes of death. Regarding treatment-related deaths, rates due to SMNs are high among the youngest patients (aged below 4 years) at cancer diagnosis, among those exposed to radiation, and after the administration of alkylating agents or high-dose epipodophyllotoxins (Armstrong et al. 2009). Childhood cancer survivors were at greater risk of all non-malignant causes of death than the general population.

Another large-scale study of British childhood cancer survivors aged below 15 years at diagnosis reported that 74% of deaths were due to recurrent and 7% to secondary malignancies (Robertson et al. 1994). More than 75% died from recurrent malignancies after being diagnosed with childhood ALL, CNS, malignant bone tumor, and soft tissue sarcoma. The most recent population-based study of the British Childhood Cancer Survivor Study (BCCSS) reported an overall SMR of 10.7, and a threefold higher SMR than the general population up to 45 years from cancer diagnosis (Reulen et al. 2010). The absolute excess risks for death from recurrent cancer decreased over time, while the excess risks for SMNs and circulatory diseases increased during follow-up beyond 45 years (Reulen et al. 2010). The cumulative mortality from circulatory diseases increased from 0.8% at 30 years to 3.9% at 50 years from diagnosis. The rising tendency after 30 years was due to death due to cardiac, external, and respiratory conditions reaching 2% cumulative mortality at 50 years from diagnosis (Reulen et al. 2010). Long-term follow-up studies exceeding 20 years from cancer diagnosis offer particularly valuable insights into the changing mortality trends of cancer survivors. The mortality associated with other causes than recurrent malignancy probably represents the late effects of the cancer treatments, with the exception of those SMNs due to familial cancer syndromes, *e.g.*, the Li Fraumeni syndrome and heritable retinoblastoma (Yu et al. 2009).

According to a population-based childhood cancer survivor study from the Nordic countries, the survivors' overall SMR of 10.8 and the cumulative mortality of 14% at 25 years were similar to the CCSS and BCCSS findings (Mertens et al. 2001, Moller et al. 2001). Lower figures were reported for the proportions of deaths (7.1%) and SMR (4.9) due to subsequent cancer compared to the CCSS (SMR 15.2), which may be due to inclusion of the earlier diagnosis period than 1970 in the Nordic study (Moller et al. 2001). The most recent childhood cancer survivor study from the Nordic countries recorded an even lower overall SMR of only 8.3 and also reported the effect of three treatment eras from 1960 until 1999 (Garwicz et al. 2012). Cumulative mortality decreased after the treatment period 1960–1969, particularly among leukemia and HL

survivors, while a significant trend occurred in CNS tumor survivors only after 1990. The initial malignancy was associated with the highest proportions of causes of death in leukemia, CNS tumors, and HL survivors (79.4%, 65.8%, and 42.1%) followed by the further mortality causes, such as SMNs (14.7%, 6.5% and 21.7%) and nonmalignant deaths (14.7%, 27.7% and 36.2%) in these diagnosis groups, respectively. There were clear diagnosis-specific differences in SMRs, reflecting the effect of the primary cancer diagnosis and the associated treatment protocols on the mortality patterns (Garwicz et al. 2012). Non-cancer deaths included also external causes, such as injuries, poisonings, suicide, and accidents, in addition to cardiovascular and respiratory disease. While cardiac ischemic disease, cardiomyopathy, and pneumonia were the leading nonmalignant death causes in HL survivors, external causes, such as injuries, poisonings, and accidents, as well as pneumonia and cerebrovascular conditions prevailed in CNS tumor survivors. Some of these negative outcomes, such as death from external causes, may be due to impaired cognitive function after irradiation to the brain.

In line with the morbidity findings, the childhood diagnoses of leukemia, HL, and CNS tumors are related to the highest number of premature deaths (Garwicz et al. 2012). Overall cumulative mortality depends on the initial cancer diagnosis, and in the study of Garwicz et al. a maximum of 27% mortality at 30 years in HL survivors was reported; after this observation time, nonmalignant causes exceeded cancer-related mortality. The SMRs for any malignant, nonmalignant, and circulatory deaths followed similar trends in the three age-groups. In contrast to this, the SMR for respiratory conditions was only elevated in the youngest and oldest subgroup of cancer survivors, apparently due to the low number of respiratory deaths. As cardiovascular late effects are potentially lethal and may be treated early or even prevented, long-term screening for non-malignant diseases is a crucial aspect of the follow-up of childhood cancer survivors.

2.3.2 Mortality of young adult cancer survivors

Only a few studies have focused on the excess mortality of YA cancer survivors (Bhuller et al. 2016). A population-based investigation on mortality in cancer survivors below the age of 35 years at diagnosis in Finland shed light on this topic (Prasad et al. 2012). In this study of childhood, adolescent, and YA cancer survivors, elevated SMRs decreased with increasing age at diagnosis in the age subgroups 0–14, 15–19, and 20–34 years compared to the general population (SMR 9.3, 5.9, and 4.6, respectively) with an overall SMR of 7.3 for the total cohort (Prasad et al. 2012). The cohort's overall SMRs were highest for deaths due to malignant disease (SMR 18.2), followed by circulatory and respiratory death causes (SMR 1.9 and 2.1). In general, younger age at diagnosis predisposed to higher SMRs. With respect to diagnosis-specific SMRs, the highest significant SMR values were observed in CNS tumor, NHL, and HL survivors due to nonmalignant disease (Prasad et al. 2012). Regarding the highest circulatory disease-related SMRs, NHL and HL survivors had five and seven-fold higher mortality ratios than the general population, in analogy to their previously observed increased cardiovascular morbidity. Only CNS tumor survivors had elevated risks for death from

cerebrovascular conditions. Respiratory disease related SMRs were greatest after following a diagnosis of HL or CNS tumors (Prasad et al. 2012).

A population-based study from Canada reported mortality trends among survivors of a narrower age range of YA cancer survivors, 20 to 24 years at diagnosis (Zhang et al. 2012). The YA cancer survivors' overall SMR was high compared to the reference population in British Columbia (SMR 5.9; 95% CI 4.9-6.9). In this study, the highest overall values were recorded among CNS tumor survivors (SMR 23.6). Among specific cancer diagnoses, only CNS tumors were associated with an increased HR for death from all causes (HR 3.4; 95% 2.1-5.7). Radiation exposure, male gender, and relapse within five years from diagnosis were associated with elevated HRs for death (Zhang et al. 2012).

In addition to studies on the causes of death in large childhood or YA cohorts of a variety of cancer diagnosis, many investigations have focused on specific cancer diagnosis groups. Especially in long-term survivors of HL, cardiovascular diseases have turned out to be the most common nonmalignant causes of death (Aleman et al. 2003). The SMR due to myocardial infarction was strikingly higher among British HL survivors aged below 25 years at cancer diagnosis than among those aged 25–34 years at diagnosis (SMR 18.7 and 5.9, respectively) in a large study of HL patients (Swerdlow et al. 2007). Moreover, an attained age below 45 years was associated with the highest myocardial infarction-related SMR (SMR 8.5) during follow-up. The SMR for this death cause for the entire HL cohort, including adults, was highest during the first year after therapy (SMR 4.2), but remained markedly higher than among general population at the end of follow-up, more than 25 years from cancer diagnosis (SMR range 1.7-4.1 and 2.8 at the end of follow-up). One year after the diagnosis, the SMR declined only to peak again at 15–19 years from diagnosis (SMR range 4.1). This shows the necessity of very long-term follow-up in this diagnosis group (Swerdlow et al. 2007).

With respect to radiation therapy, the highest SMR was associated with total nodal therapy (SMR 9), followed by mantle therapy (SMR 3.2), and other supradiaphragmatic therapy (SMR 2.3). Regarding chemotherapy, the exposure to anthracycline was associated with an elevated SMR (2.9) due to myocardial infarction, especially after treatment with the ABVD combination (doxorubicin, bleomycin, vinblastine, and dacarbazine) (SMR 9.5). The combination of supradiaphragmatic irradiation with numerous chemotherapeutic agents potentiated the impact on the myocardial infarction-related SMR. Among the entire HL patient cohort, the subcohort of under 35-year-olds at diagnosis had higher SMRs due to myocardial infarction compared to the older patients in all treatment modality combinations (Swerdlow et al. 2007).

Another study of early-stage HL patients aged below 50 years at diagnosis concluded that the relative risk for cardiac mortality rose significantly after 20 years from diagnosis (RR 4.4), while the relative risk for death from a second cancer declined after this time period, emphasizing the long-term impact of treatment on this specific cause of death (Ng et al. 2002). Hence, these diagnosis-specific findings stressed the importance of

cardiac screening and monitoring among early onset cancer survivors, particularly among HL survivors who are at a great risk of cardiac death.

In addition to studies on mortality in early onset HL survivors, a large study from North America and Europe on testicular cancer survivors below the age of 35 years at cancer diagnosis demonstrated that their overall SMR (SMR 1.16, 95% CI 1.08-1.25) for non-cancer causes was slightly higher than among the general population (Fossa et al. 2007). Regarding cause-specific deaths, the highest SMRs occurred for infections (SMR 1.57, 95% CI 1.25-1.96), circulatory diseases (SMR 1.23, 95% CI 1.09-1.39), and all cardiovascular diseases (SMR 1.19, 95% CI 1.03-1.37) (Fossa et al. 2007). With respect to treatment-related SMRs among those younger than 35 years at cancer diagnosis and treated after 1975, the overall non-cancer-related SMR was elevated after radiotherapy only (SMR 1.21, 95%CI 1.01-1.44). Interestingly, significantly elevated SMRs among this younger subgroup occurred for infections after chemotherapy only (SMR 2.61, 95% CI 1.59-4.03) and for circulatory disease after radiation only (SMR 1.70, 95% CI 1.21-2.31) compared to the general population (Fossa et al. 2007).

2.4 CARDIOTOXICITY OF CANCER TREATMENT

The past three decades have brought about great improvements in childhood and adulthood cancer therapies (Karim-Kos et al. 2008, Madanat-Harjuoja et al. 2014). With increasing numbers of childhood cancer survivors, the late effects of cancer treatment have become more evident and are concerning (Oeffinger et al. 2006, Hudson et al. 2013). Especially the introduction of combination therapy involving multimodal approaches, such as chemotherapy, radiation therapy, and surgery, have led to improved cancer survival, but also to a higher risk for adverse outcomes (Figure 3). Cardiotoxicity has been recognized as one of the most serious consequences of antineoplastic therapy (Yeh et al. 2009, Albini et al. 2010). Despite survival from cancer, cardiac complications after antineoplastic therapy can severely reduce the survivors' quality of life and are the leading non-malignant cause of death (Reulen et al. 2010, Prasad et al. 2012, Zhang et al. 2012). Cardiovascular adverse events can be manifold and may manifest as cardiomyopathy, pericarditis, cardiac insufficiency, valvular disease, and premature coronary artery disease (Krischer et al. 1997, Aleman et al. 2007) (Figure 3).

In addition to chemotherapy, radiation therapy predisposes to cardiovascular sequelae, such as accelerated atherosclerosis, vascular stenosis, thromboembolism, transient ischemic attack, and stroke (Adams et al. 2005, Bowers et al. 2006). Besides direct effects on the heart, chemotherapeutic drugs may act on the coagulation system and promote thrombosis and thrombotic events (Albini et al. 2010). Venous thromboembolism may be associated with chemotherapy including alkylating agents, asparaginase, antiangiogenic drugs, such as thalidomide, and tyrosine kinase inhibitors (Albini et al. 2010).
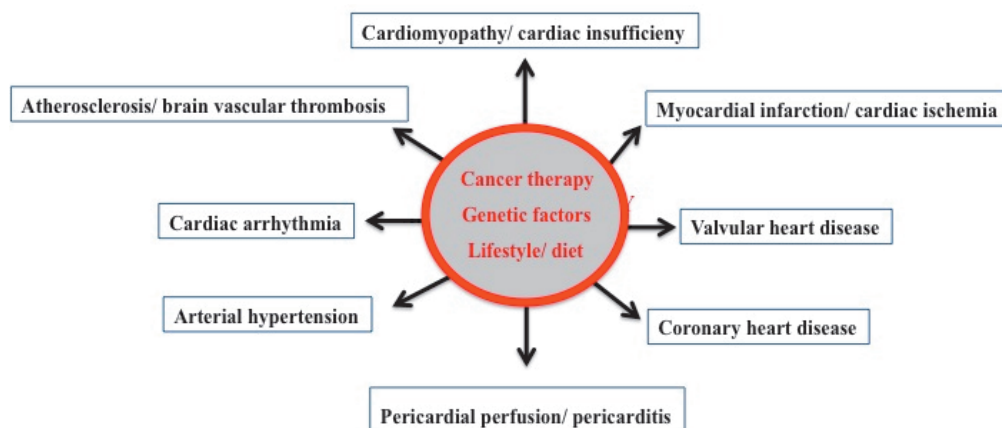
Figure 3: Cardiovascular late effects after early onset cancer

While cardiotoxicity was originally associated with the use of anthracyclines, a wide range of other chemotherapeutic drugs, e.g., alkylating agents (etoposide), antimetabolites (methotrexate, 5-fluorouracile), retinoids (isoretinoin), antimicrotubule agents (estramustine), diverse antitumor agents (bleomycin), cytokines (interleukin-2), cytotoxines (arsenic trioxide), proteasome and tyrosine kinase inhibitors, and immunomodulatory drugs (thalidomide) have since then been identified as causes for negative cardiovascular effects (Yeh et al. 2009, Senkus et al. 2011).

2.4.1 Anthracycline-associated cardiotoxicity

The discovery of anthracyclines during the late 1960s started the wide use of an effective antineoplastic drug class for cancer treatment (Tan et al. 1967). The most common anthracyclines administered for cancer treatment are daunorubicin, doxorubicin, epirubicin, and idarubicin. Among anthracycline antibiotics, doxorubicin and daunorubicin are used most frequently (Albini et al. 2010). Whereas doxorubicin has been a cornerstone of various therapies targeting breast cancer, childhood solid malignancies, soft tissue tumors, ALL, and lymphomas, daunorubicin has been a powerful player in the treatment of both ALL and AML (Minotti et al. 2004). Later on, the anthracenedione drug class, typically mitoxantrone, with similar cell toxic effects has been used in cancer therapy.

While the precise mechanism of action of anthracyclines on cancer cells remains unclear, many pathways may convey the cytotoxic action of this drug class. Anthracyclines affect cancer cells in several ways by inhibiting DNA and RNA synthesis, intercalating into the DNA strands, releasing free oxygen radicals that damage the cell membrane and mitochondrial DNA (especially in cardiomyocytes), inhibiting topoisomerase II, interfering with the iron homeostasis of cardiomyocytes, and promoting cell death (Minotti et al. 2001, Minotti et al. 2004, Lebrecht et al. 2005, Wojnowski et al. 2005). The initial success of this class of drugs led to its widespread

use in cancer therapy, but cardiac complications became quickly apparent as potentially lethal and apparently dose-dependent side effects (Von Hoff et al. 1979). A mean cumulative anthracycline dose of more than $300mg/m^2$ increases the risk for clinical heart failure after childhood cancer treatment (Kremer et al. 2001), but cardiac late effects have been reported after doses as low as $45mg/m^2$ (Lipshultz et al. 2005). This observation implies genetic factors as being involved in the risk for cardiotoxicity. Childhood cancer survivors are at higher risk for cardiovascular adverse conditions than their siblings even without radiation or anthracycline exposure (Lipshultz et al. 2012), since chemotherapeutic drugs other than anthracyclines may lead to cardiotoxicity. This explains the elevated risks for cardiovascular late effects in childhood cancer survivors.

The negative effects of anthracyclines have been thoroughly studied, since they have a strong impact on premature cardiovascular morbidity and mortality. Anthracycline-induced cardiotoxicity can be classified into two main categories according to the time of onset: the rare acute and the more common chronic form of cardiotoxicity (Kremer et al. 2001, Wouters et al. 2005, Harake et al. 2012) (Figure 4). Chronic cardiotoxicity may present as the early onset variant and as the late onset chronic progressive variant, which are encountered by 2% and 5%, respectively, of childhood cancer survivors (Kremer et al. 2001). In the asymptomatic phase of chronic cardiotoxicity, compensation of cardiac damage by morphological changes, such as cardiac hypertrophy, may mask injuries to the cardiac tissue (Suter et al. 2013) (Figure 5). However, as the time from the cardiotoxic drug exposure increases, the contractile function of cardiomyocytes may rapidly decrease and become symptomatic (Figure 5). The chronic late onset form is associated with heart failure in up to 16% of childhood cancer survivors even more than 20 years from the initial anthracycline exposure (Kremer et al. 2002 B). Female gender, young age at cancer diagnosis, and certain ethnicity (Hispanic or black) are associated with an increased risk for cardiovascular late effects (Lipshultz et al. 1995).

Anthracycline-induced cardiotoxicity

Acute cardiotoxicity

Immediately (<3 days) after exposure

-Transient symptoms: QT-changes, abnormal supra-/ventricular repolarization, acute coronary and peri-/myocarditis-like syndromes
-Not dose-dependent.
-Rare and reversible.

LV: left ventricular

Chronic cardiotoxicity

Early onset (<1 year after exposure)

-Progressive LV dilation and LV wall thinning, decreased cardiac contractility.
-Also at lower anthracycline doses (<120mg/m²).
-Cardiomyocyte death (apoptosis, necrosis).
-More common and irreversible.

Late onset (>1year after exposure)

-LV dysfunction, arrhythmia, heart failure.
-Cardiomyocyte death (apoptosis, necrosis).
-Partially dose dependent, genetical risks suggested.
-Cardiomyocyte death (apoptosis, necrosis).
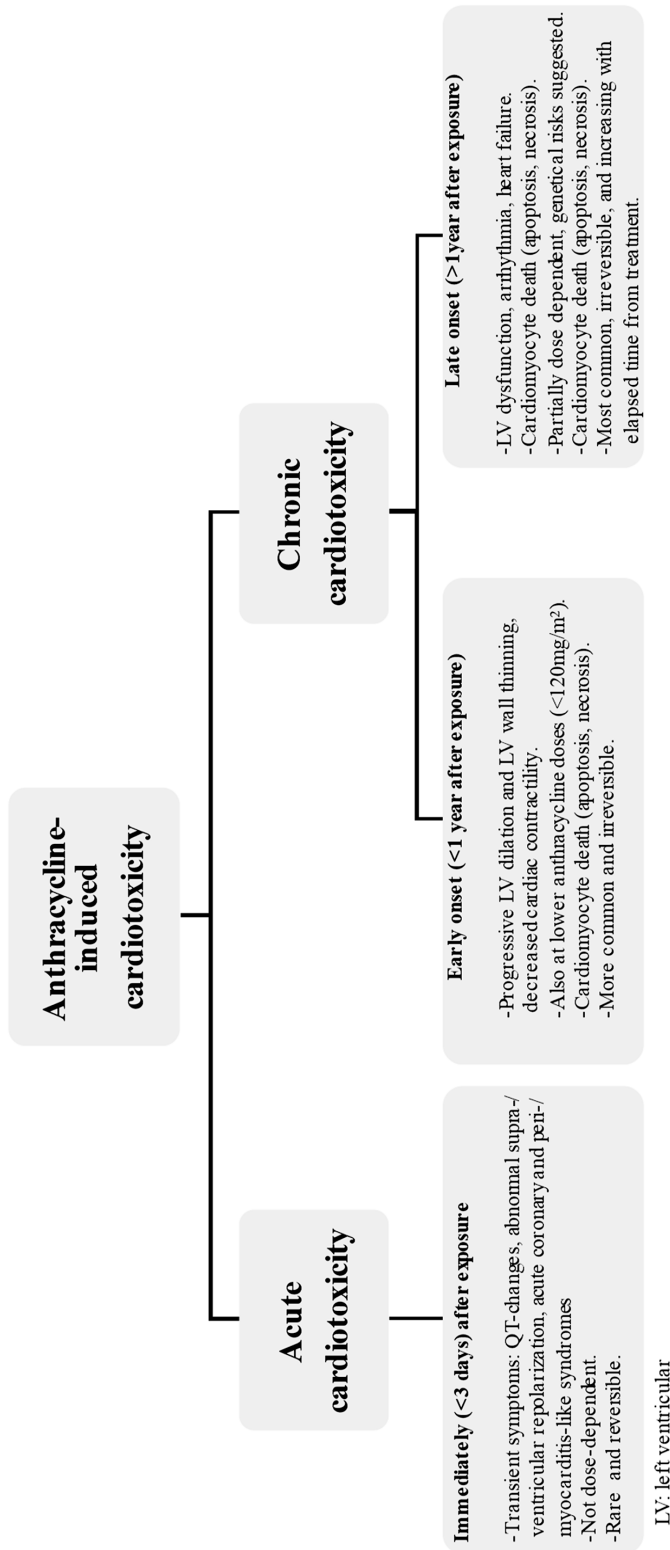-Most common, irreversible, and increasing with elapsed time from treatment.

Figure 4: The major types of anthracycline-induced cardiotoxicity can be categorized by time of onset: acute, chronic early onset, and chronic early onset. The most common form is late onset cardiotoxicity that may intermittently be asymptomatic for even more than 20 years from anthracycline exposure.
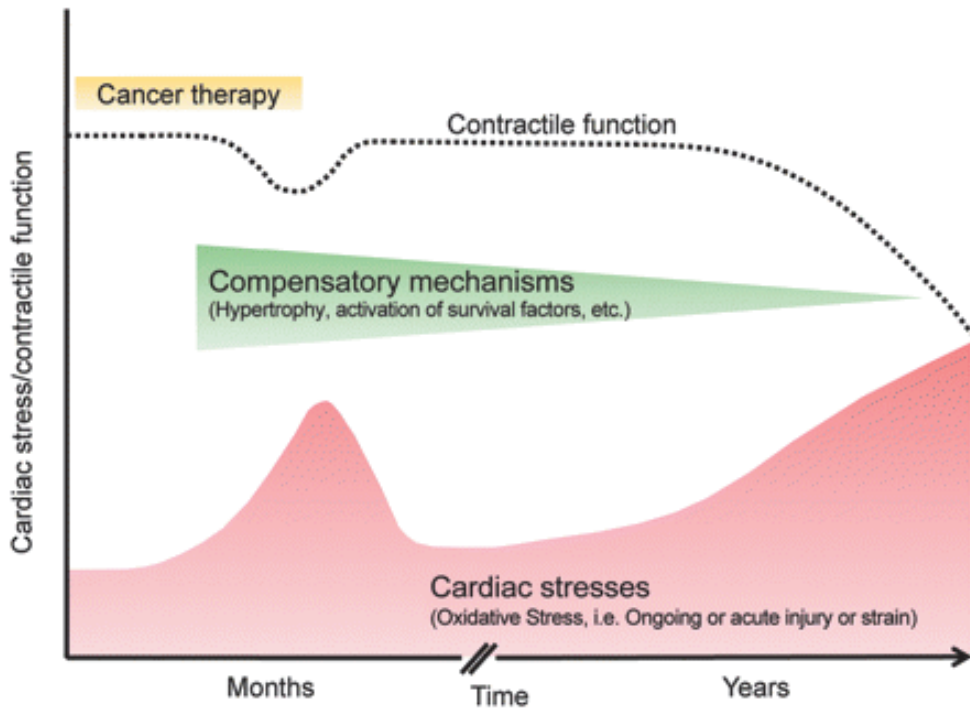
Figure 5: Cardiac dysfunction (in terms of cardiac contractile function) after cancer therapy with cardiotoxic medication, *e.g.*, anthracyclines by time (months to years) after cancer therapy. Adapted from Suter et al. and reprinted with permission of Oxford Journals Publishing (Suter et al. 2013).

The morphological changes of anthracycline-associated cardiomyopathy resemble those of dilated cardiomyopathy. Endomyocardial biopsies of cancer survivors with this form of cardiomyopathy have revealed structural changes in cardiomyocytes: enlargement of the sarcoplasmic reticulum and mitochondria, vacuolization in the cytoplasma, reduction of myofibrils, and numerous lysosomes (Minotti et al. 2004). All heart chambers may appear dilated and mural thrombi can be frequently found in both ventricles (Takemura et al. 2007). Although precise pathogenetic mechanisms leading to acute heart failure and cardiotoxicity remain yet to be elucidated, various hypotheses have been proposed, including lipid peroxidation, excess oxidative stress, reduced levels of antioxidant and sulfhydryl groups, and increased release of reactive oxygen species (ROS) (Takemura et al. 2007, Bollard et al. 2013) (Figure 5). Since antioxidant enzymes are less prevalent in the heart tissue compared to other organs, the increased level of ROS may lead to the myocardial damage, myocardial cell death, and, possibly, irreversible heart failure (Chatterjee et al. 2010). It has also been suggested that anthracyclines may induce apoptotic cell death in myocardial as well as endothelial cells (Kotamraju et al. 2000) (Figure 5). Figure 6 summarizes the pathomechanisms leading to cardiovascular damage following exposure to chemotherapeutic drugs or radiotherapy.
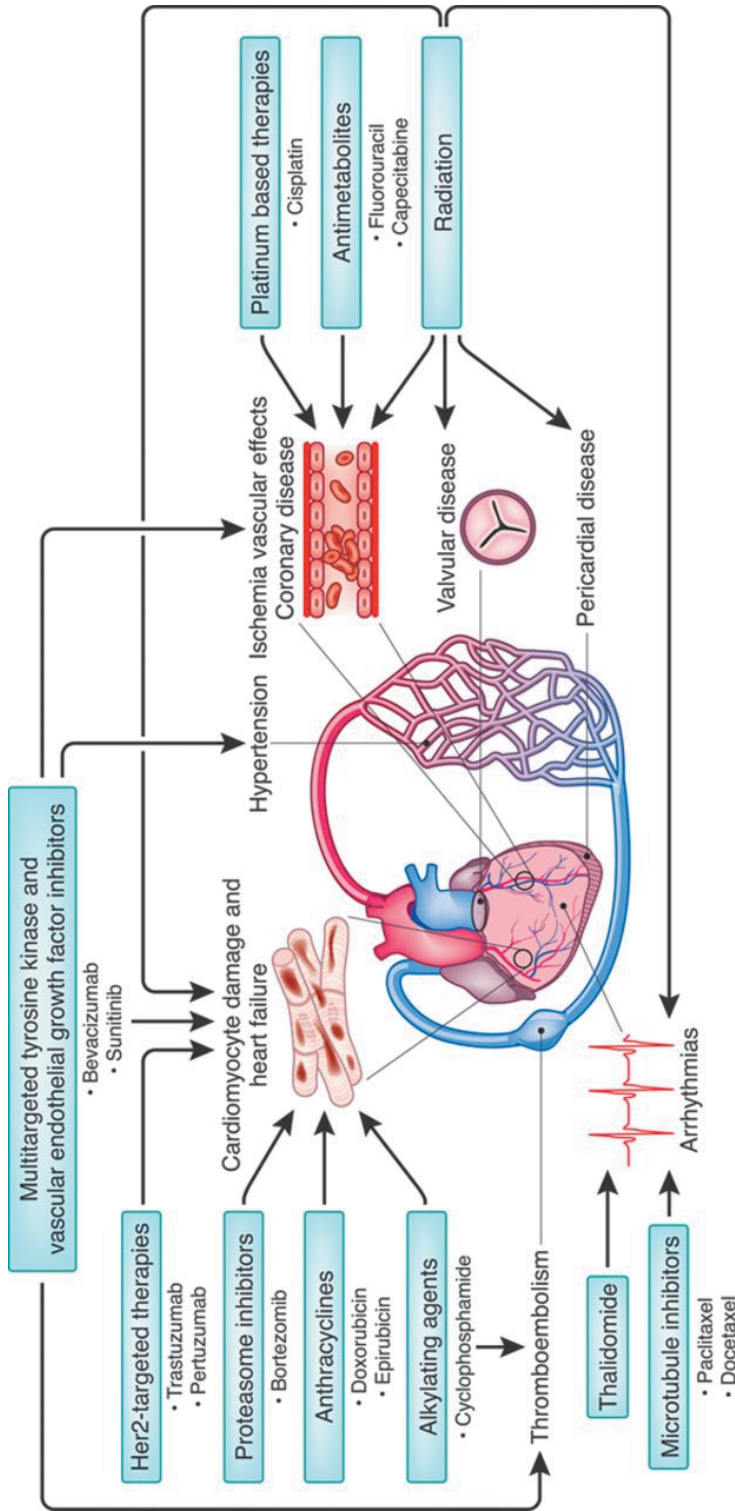
Figure 6: Effects of different forms of cancer therapy (chemotherapy and irradiation) on the cardiovascular system. This overview illustrates the various pathomechanisms leading to cardiovascular complications after cancer treatment. Adapted by Lenneman and colleagues (Lenneman et al. 2016) and reprinted with permission of the American Heart Association.

2.4.2 *Radiation-induced cardiomyopathy*

In addition to chemotherapy and surgery, radiation therapy has been a cornerstone of cancer treatment for about a century (Hudson et al. 2012). About half of all cancer patients receive radiotherapy today (Yusuf et al. 2011). Radiation-associated heart disease may manifest as radiation-induced arteriosclerosis, pericarditis, pericardial effusion, cardiomyopathy, valvular disease, or cardiac conduction disturbances (Figure 6). The precise mechanisms underlying radiation-induced vascular disease are not fully known. The consequences of radiation therapy, such as endothelial damage, lysosomal activation, and the infiltration of arteries with lipid and inflammatory cells have been reported (Yusuf et al. 2011). ROS are generated by radiation, which has been demonstrated in rats with increased levels of superoxide and peroxides in their microvessels (Hatoum et al. 2006). The radiation of mice has also shown to accelerate the development of macrophage-rich, atherosclerotic lesions. Radiation may cause this damage to the cardiac tissue by injuring endothelial cells of the capillaries, which leads to the obstruction of the capillary diameter, which ultimately results in thrombus formation (Adams et al. 2005). Myocardial perfusion defects emerge and these may progress to myocardial fibrosis, diastolic dysfunction, and, finally, heart failure (Adams et al. 2003). To reduce the high occurrence of late toxicity due to photon radiotherapy, proton beam therapy has been introduced as an alternative to reduce the toxicity of this type of treatment (Mizumoto et al. 2016).

The combination of other cardiovascular risk factors, such as smoking and hyperlipidemia, can potentiate the risk of cardiovascular disease after exposure to irradiation (Armstrong et al. 2013). It is important for cancer survivors to follow lifestyle recommendations, such as a healthy diet, physical activity, and abstinence from tobacco and nicotine, to reduce the risk for cardiovascular late effects (Knobf et al. 2011).

Radiation therapy may affect other organ systems than the heart, which may indirectly affect heart function. Pulmonary fibrosis may result from mediastinal radiation and from exposure to certain chemotherapeutic agents, e.g., bleomycin, busulfan, carmustine, or lomustine (Mertens et al. 2002). Additionally, radiation may lead to the stenosis and/or fibrosis of the carotid arteries, the aorta, or pulmonary branch arteries. As a consequence, this may clinically manifest as stroke, transient ischemic attacks, vertebrobasilar insufficiency, and ischemia of the upper or lower extremities (Adams et al. 2005).

Mediastinal radiation causes cardiovascular late effects, putting especially HL survivors at a high risk for these adverse outcomes (Donaldson et al. 1982, Aleman et al. 2007, Castellino et al. 2011) (Figure 6). A study showed that among HL survivors of a wide age range at diagnosis treated with radiation, an age below 35 years at diagnosis was associated with higher standardized mortality ratios related to myocardial infarction compared to the general population (Swerdlow et al. 2007). A large study of childhood HL survivors reported an increased risk for radiation-induced cardiac complications above the radiation dose of 36 Gray (Schellong et al. 2010). After radiation therapy for breast cancer, endothelium-dependent vasodilation is decisively reduced in the irradiated axillary arteries

compared to the unexposed arteries (Beckman et al. 2001). Despite advances in radiation techniques to reduce cardiovascular complications, the risks for congestive heart failure and valvular disease are still high after mediastinal radiation (Hull et al. 2003).

2.5   METABOLIC SYNDROME AFTER CANCER AT A YOUNG AGE

The metabolic syndrome (metS) is defined as a cluster of three or more of the following findings: glucose intolerance, central obesity, arterial hypertension, and dyslipidemia (either increased triglycerides and low-density lipoprotein or decreased high-density lipoprotein cholesterol) (Alberti et al. 2009). With respect to children and adolescents, the definition of metS has been discussed, but there is no general definition of metS for this young patient group yet (Zimmet et al. 2007). The following clinical findings comprise traits of the metS and have served as clinical outcomes in previous pediatric studies: high body mass index, arterial hypertension, high fasting blood insulin, high fasting blood glucose, high levels of LDL and low levels of HDL cholesterol, and high triglycerides. Cranial as well as total body irradiation and chemotherapy are associated with an increased risk for metS, which is related to growth hormone deficiency, hypothyroidism, gonadal dysfunction, hypomagnesemia, obesity, and abnormal glucose metabolism (Taskinen et al. 2000, Taskinen et al. 2007). The clinical features associated with the metS are risk factors for cardiovascular disease and may lead to excess cardiovascular mortality (Gami et al. 2007, Siviero-Miachon et al. 2008). A Finnish study was the first to demonstrate a higher likelihood for features of the metS after childhood cancer compared with healthy controls (Talvensaari et al. 1996).

Pediatric cancer treatments, including HSCT, are a risk factor for the metS, in addition to other known causes, such as physical inactivity and obesity (Taskinen et al. 2000, Smith et al. 2014, Wilhelmsson et al. 2015). Childhood CNS tumor and ALL survivors are at risk for obesity and hypertension (Pietila et al. 2009, Gurney et al. 2003, Gurney et al. 2006, Gunn et al. 2015). Furthermore, the risk for acquiring traits of the metS is associated with many other childhood cancer diagnosis groups (Gurney et al. 2006, Siviero-Miachon et al. 2008, Holmqvist et al. 2014). The risk for type 2 diabetes is increased after childhood cancer (Taskinen et al. 2000, de Vathaire et al. 2012, Holmqvist et al. 2014), which contrasts to the fact that type 1 diabetes is the predominant form of diabetes in healthy children (Craig et al. 2014). While radiation to the pancreatic area and asparaginase administration may damage the beta cells of the pancreas and reduce insulin secretion, the precise pathomechanisms underlying the developing type 2 diabetes in childhood cancer survivors are unknown (de Vathaire et al. 2012).

Almost one third of childhood cancer survivors show clinical findings associated with the metS (arterial hypertension, increased fasting glucose, low HDL levels, and enlarged waist circumference), and almost 90% of those who do not adhere to the suggested life style changes may present with symptoms of the metS (Smith et al. 2014). Hence, regular and lifelong follow-ups are imperative for the prevention the cardiovascular

risks associated with the metS, especially in the growing population of childhood and YA cancer survivors who are at risk (Armstrong et al. 2013). Interventional studies promoting physical fitness and a healthy lifestyle have produced beneficial effects on reducing cardiovascular risk factors, also the metS, in both childhood and adult cancer survivors (Knobf et al. 2011, Jarvela et al. 2012).

2.6   LONG-TERM FOLLOW-UP GUIDELINES (LTFU) AFTER CHILDHOOD AND YOUNG ADULT CANCER

Although methods and study criteria have not been uniform regarding the age at diagnosis, the diagnosis spectrum, and a coexisting morbidity, one conclusion is indisputable: survivors of childhood and YA cancers require specific long-term health screenings and follow-up. A recent North American childhood cancer survivor study showed that a substantial proportion of late effects was detected only after a specific risk-adapted medical investigation (Hudson et al. 2013). Clearly, there is a strong need for individualized risk-based health check-ups on a long-term basis after cancer survival (Hudson et al. 2013). Given the high incidence of long-term sequelae in childhood cancer survivors, several large consortia have been formed to analyze published data and formulate guidelines for the follow-up after cancer at an early age (Table 3).

The Northern American Children's Oncology Group has recommended screening of numerous known long-term effects summarized in the COG Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent and YA cancer (COG LTFUG) (Landier et al. 2004, Visscher et al. 2012, Landier et al. 2012) (Table 3). In Europe, several countries have developed national follow-up guidelines, but these differ greatly among the 50 European countries (Brown et al. 2014). The need for European uniform evidence-based guidelines became apparent in a survey on follow-up systems throughout Europe in EU and non-EU countries (Brown et al. 2014). Childhood cancer survivors in the United Kingdom are monitored according to formulated guidelines by the Children's Cancer and Leukemia Group (CCLG) (www.cclg.org.uk), the Scottish Intercollegiate Guidelines Network (SIGN) has been working on the formulation of follow-up plans in Scotland, the Swedish Working Group for Long-term Follow-up after Childhood Cancer (SALUB) in Sweden and the GPOH (German Society for Pediatric Oncology and Hematology) in Germany (Table 3).

Since it was imperative to provide guidelines for all European countries to ensure the best possible follow-up after cancer at a young age, European pediatric oncologists and specialists initiated the Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer (PanCare) in 2008 (Hjorth et al. 2015), (www.pancare.eu). Thereafter, the 6-year PanCare Childhood and Adolescent Survivor Follow-up project (PanCareSurFup) was started in 2011 to address late effects after cancer at a young age (http://www.pancaresurfup.eu/about-pancaresurfup). The most recent project, the 5-year PanCare LIFE project, was founded in 2013 to investigate fertility disturbances,

ototoxicities and the quality of life of survivors aged up to 25 years at cancer diagnosis (http://www.pancarelife.eu/project/). Another goal was to create an individual passport for childhood and adolescent cancer survivors to ensure appropriate lifelong health controls and also to empower cancer survivors to secure long-term check-ups by being informed about the cancer diagnosis and the individual treatment history (http://www.pancare.eu/documents/meetings/genova-2013/pancare-genoa-presentations/ session-2/haupt-riccardo-ortotali-maurizio-pancare-genova-survivorship-passport.pdf).

In Finland, a long-term follow-up system for early onset cancer survivors was implemented in 2016. Each of the five Finnish university hospitals have created their own institutional program of medical and psychosocial follow-ups for childhood cancer survivors. As a part of the national cancer center's (FICAN) project, the Turku University Hospital launched a pilot study (named STEP) in 2015 to follow up late effects among adult survivors of childhood and adolescent malignancies. So far, the STEP project has targeted survivors with a diagnosis of cancer below the age of 18 years and who have treated at the pediatric unit since 1980. After completion of their follow-up at the pediatric unit (usually by age 18), cancer survivors will receive a passport containing the critical information on their prior cancer therapy and the main concerns for their medical long-term and, possibly, lifelong surveillance. These survivors are also invited to the STEP-project for physical examinations or digital surveillance, depending on their estimated risk for late adverse health effects. There are plans to expand this follow-up care to a broader age range of cancer survivors with a diagnosis of cancer before age 25 years (http://www.vsshp.fi/fi/toimipaikat/tyks/to8/to8c/Sivut/default.aspx).

The ultimate goal is to globally collect long-term data on childhood cancer survivors. Efforts were made in 2010 to establish an international consortium for this purpose, the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) (Kremer et al. 2013). The International Society for Pediatric Oncology (SIOP) aims to advocate the fight against childhood cancer also by promoting research. The increase in cancer awareness and the cooperation with childhood cancer survivors and their families makes the assembly unique. The consortium of doctors, scientists, cancer survivors, and their families create a multidisciplinary consortium, the aim of which is to improve every aspect of childhood cancer, from diagnosis to long-term follow-up after treatment. The European unit, SIOPE, promotes the equal availability of treatment after cancer at a young age regardless of the patient's domicile (Vassal et al. 2014). Recently, follow-up guidelines for survivors aged up to 25 years at cancer diagnosis have been discussed and the PanCare LIFE project plans to expand the age range at cancer diagnosis to an older age.

In the future, it will be crucial to formulate guidelines for the follow-up of YA cancer patients. This currently poses a challenge, since further research on late complications is needed as a basis for formulating specific guidelines (Marris et al. 2011). In 2006, a workshop from the Institute of Medicine for setting up long-term surveillance of adult cancer patients has been held, but general guidelines remain to be established (https://www.nationalacademies.org/hmd/Reports/2006/Implementing-Cancer-Survivorship-Care-Planning-Workshop-Summary.aspx).

Table 3: Long-term follow-up (LTFU) guidelines by country/ group and their criteria. CPG: clinical practice guideline

Name	Area	Criteria Age at diagnosis	Diagnosis time	established	Characteristics
COG **Children Oncology Group**	North America	<21y (>2y treatment)	1996-2002	2004	Categories of consensus, hospital-based, CPG
UKCCSG/CCLG **UK Children's Cancer Study Group (Cancer and Leukemia Group)**	UK	<15y	1977-2012	1977/ 2006	Multidisciplinary experts, population-based
SIGN **Scottish Intercollegiate Guidelines Network**	Scotland	<15y (<24y) N=3,235	1983-2007	1993 (2011 Cancer)	Multidisciplinary, population-based
DCOG LATER **Dutch Children Oncology Group**	Holland	<18y N=6,168	1963-2002	2012	Questionnaires, medical records, physical examination, laboratory tests, nationwide hospital-based
SALUB **Swedish Working Group for Long-term Follow-up after Childhood Cancer**	Sweden	<15y N=7,065	1984-2010	2007	Population-based
GPOH **German Society for Pediatric Oncology and Hematology**	Germany	<18y N=37,291	1980-2008	2006	Cancer registry population-based
PanCareSurFup **Pan Care Survivor Follow-up**	Europe (16 countries)	<21y, N>100,000	1940s-2000s	2011	Retrospective observational European-wide study, partially case-control study
PanCareLIFE **Pan-European Network for Survivors of Childhood and Adolescent Cancer**	Europe	<25y N>12,000	2000s	2013	Observational, molecular genetic analysis
IGHG **International Late Effects of Childhood Cancer Guideline Harmonization Group**	11 representatives	Not specified, Childhood cancer in general	Not specified	2010	Worldwide, common guidelines for follow-up to increase the quality of life after cancer, CPGs

3   AIMS OF THE STUDY

The aims of this thesis were to elucidate the cardiovascular late adverse health effects and mortality after cancer at an early age compared to siblings and the general population. Information on this topic is necessary to modify and improve the guidelines for long-term cardiovascular surveillance of childhood cancer survivors and to set up the yet lacking cardiovascular follow-up recommendations for young adult cancer survivors.

The following topics were addressed:

* *   To assess any difference in cardiovascular morbidity between early onset cancer survivors and siblings via linkage to the hospital discharge registry.

* *   To assess the purchase of cardiovascular drugs and medications associated with the metabolic syndrome in early onset cancer survivors and siblings.

* *   To elucidate the differences in standardized mortality ratios and causes of death between early onset cancer survivors and the controls.

* *   To investigate the impact of treatment era, cancer diagnosis, and age at cancer diagnosis on cardiovascular adverse sequelae later in life.

* *   To analyze the cumulative incidence of cardiovascular late complications and excess cardiovascular mortality in early onset cancer survivors and siblings during a long follow-up.

4 SUBJECTS, PATIENTS, MATERIALS, AND METHODS

4.1 REGISTRIES ACCESSED IN THIS THESIS

4.1.1 *The Central Population Register (CPR)*

Data from the Finnish Population Information System and from local register offices are collected by the PRC. The national PRC was founded in 1969 and computer-based registration began in 1971.

Since 1967, every Finnish resident has received a unique personal identity code (PIC), with which various aspects of everyday life are recorded, including health care service, and personal data. Basic personal information can be retrieved by the PRC, such as first and last name, any former names, the PIC, the address, the municipality of residence, the citizenship, family relations (spouse, siblings, children), the date of birth, and, if applicable, death or emigration. Links to parents, siblings and children have been available for family members born after 1955. Siblings of cancer patients were identified by linking the patient's PIC to his/ her parents and by listing all children of the parents.

4.1.2 *The Finnish Cancer Register (FCR)*

The nationwide Finnish Cancer Register (FCR) was founded in 1952 and the documentation of information on all cancer cases in Finland started in 1953. In 1961, the National Board of Health passed a law to make the report of all nation-wide cancer cases by physicians, hospitals or other institution compulsory. Further notifications with respect to the tumor site and histology are provided by specialized laboratories. Moreover, information on death certificates concerning malignancies are reported by Statistics Finland to enable a nearly complete coverage of malignancies (100% of childhood cancers, 99% of solid tumors, and 92% of hematological cancers) (Teppo et al. 1994).

The FCR collects the following data concerning cancer cases: the patient's name and PIC, the municipality of residence, the primary cancer site, the date of diagnosis, the cancer stage (localized, regional metastases, distant metastases, if applicable), the malignancy feature (malignant, microinvasive, in situ, borderline, benign (e.g. intracranial, urinary tract) and any exclusion criteria from basic statistics (e.g. basalioma, polycythemia vera, myelofibrosis)), the malignant histology/ cell type, the treatment (surgery, radiotherapy, cytotoxic drugs, hormones, other; specific codes for curative/palliative surgery or radiotherapy; specific codes for primary treatment and later treatment) and the follow-up (date of death or emigration and cause of death, if applicable). Specific details on the cancer therapy are not available via the FCR.

The causes of death in cancer patients and the general Finnish population are reported to the FCR via automated record linkage by Statistics Finland. After that, the FCR

validates the official cause of death of each cancer patient by retrieving all available information. This procedure aims to exclude patients that died from another cause of death than primary cancer. Mortality rates released by the FCR reveal more detailed classifications concerning cancer than Statistics Finland. After the 1980s, the data on death causes of cancer patients have been equally provided by both the FCR and Statistics Finland.

4.1.3 The Finnish Hospital Discharge Registry (HDR)

The HDR offers information on all hospital visits in Finland since 1969 and electronic data have been available since 1.1.1975. Between 1969 and 1993, the municipal and private sector provided data concerning the main reasons of hospitalization (one or more International Classification of Diseases (ICD) diagnosis codes), the dates of arrival and departure, and the specific hospital. After 1994, out-patient treatments have also been reported. Due to the comprehensive public health care system in Finland, nearly all treatments are offered as part of public health care, especially regarding cancer therapies. The cancer patients were linked to the HDR via the PIC. The ICD codes for adverse outcomes were retrieved from the HDR. For statistical analyses, the ICD-8 and -9 codes were manually transformed to ICD-10.

4.1.4 The Cause-of-Death Register (CDR)

Statistics Finland records information on the causes of death and on the trends of mortality in the Finnish population. The CDR has archived death certificates since 1936. After 1969, information on death causes has been available in a computerized form. The register retrieves data with respect to the cause of death, the age, gender, marital status, and other demographic features. Furthermore, data are available concerning death circumstances, as well as perinatal, neonatal, and infant mortality. The statistics are presented each year according to specified causes of death determined by Statistics Finland. Since 1996, the statistics have been recorded according to the ICD-10. Before that, the death causes were classified based on the ICD used in the specific death years (ICD-8: 1969-1986, ICD-9: 1987-1995) and transformed to the diagnosis criteria of the current ICD-10. The data on death causes have been collected according to the information of the death certificates and from the PRC. Death certificates are issued either by the clinician who treated the patient or possibly the pathologist who performed the autopsy. Physicians in the provincial government and at Statistics Finland further review the death certificates and request an additional review by the physician in the case of unclarity.

4.1.5 The Drug Purchase Register (DPR)

The DPR is controlled by the Social Insurance Institution (SII) and has registered all purchased prescription drugs since 1993. The register records data on all prescription refundable medications, except for over-the-counter drugs, drugs received in hospital

care, and those reimbursed by occupational health-care funds. This database files the patients' PIC, the purchase date of the prescription drug, the price of the medication, and the package size. All drugs have been listed according to the specific categories of the Anatomical Therapeutic Chemical (ATC) codes released by the World Health Organization (WHO About the ATC/ DDD system www.whocc.no/atcddd/). Drug purchases are recorded without regard to the payer, the patient (oftentimes) or a private insurance company (seldom with the exception of children). For our studies (III and IV), we selected the first purchase of particular medications as outcome.

4.2   STUDY POPULATIONS

In this thesis, we chose four early onset cancer patient/ survivor cohorts and sibling cohorts as described in the Table 4. For the first reports (I and II), we chose 5-year cancer survivors and for the latter ones (III and IV) we selected an early onset cancer patient cohort as the study cohort.

4.2.1 The cancer survivor/patient and sibling cohorts

As shown in Table 3, the time ranges of the cancer diagnosis differed markedly within the studies due to the diverging characteristics of the respective registers that were described above.

Table 4: Overview of the studies I-IV concerning the sources for registry linkage and particular outcomes. [°°]Time period of the follow-up for the respective outcome, [1] 5-year early onset cancer survivors (aged below 35 years at cancer diagnosis), [2] Early onset cancer patients (aged below 35 years at cancer diagnosis), [^]Healthy siblings without cancer at a young age were identified via linkage to the Central Population Register (CPR), Finnish Cancer Register (FCR), Hospital Discharge Registry (HDR), Statistics Finland, cause-of-death-register, and the Drug Purchase Register (DPR)

Study	Cancer diagnosis	Study cohort	Reference cohort	Register source/ Outcome	Time period Outcome[°°]
I	1975-2004	5-year cancer survivors[1] N= 13,860	Siblings[^] N= 43,392	FCR/CPR/HDR Cardiac morbidity	1975-2008
II	1966-2004	5-year cancer survivors[1] N= 16,769	Siblings[^] N= 43,892 General population	FCR/CPR/Statistics Finland[4]/ Mortality	1971-2011
III	1993-2004	Cancer patients[2] N= 8,197	Siblings[^] N= 29,974	FCR/CPR/ DPR First drug purchase	1993-2011
IV	1994-2004	Cancer patients[2] N= 7,551	Siblings[^] N= 12,455	FCR/CPR/DPR / First drug purchase	1994-2011

We chose a healthy sibling cohort as a reference group in **Studies I-IV** to specifically investigate any impact of cancer and cancer treatment on cardiovascular adverse events. In Finland, decisive regional differences have been demonstrated regarding the familial risk for cardiovascular morbidities. The Finnish population has been described as a genetic isolate even within the country, which has been described in previous reports such as for familial hypercholesteremia (Vuorio et al. 2001). The majority of healthy siblings and cancer survivors share comparable socioeconomic backgrounds, lifestyles, eating manners and also genetic aspects. All these similarities have been observed to influence the risk for developing cardiovascular disease. As a consequence, a major difference between cancer survivors and their siblings is cancer and its therapy.

Study I: Cardiovascular morbidity in long-term survivors of early-onset cancer: a population-based study.

The 5-year cancer survivor cohort comprising 13,860 subjects was identified via linkage to the FCR. Cancer survivors met the following inclusion criteria: aged less than 35 years at primary cancer diagnosis, a diagnosis with a malignant neoplasm (including benign central nervous system (CNS) tumors and those of uncertain malignancy), primary cancer diagnosis between January 1st, 1975 and December 31st, 2004, alive at least 5 years after the initial cancer diagnosis, and not having a second malignancy before the 5-year survival. A total of 43,392 siblings served as reference group in **Study I**.

Study II: Late mortality among 5-year survivors of early onset cancer: a population-based register study.

We identified 16,769 cancer survivors younger than 35 years at primary cancer diagnosis via linkage to the FCR. The time frame of initial cancer diagnosis ranged from January 1st, 1966, until December 31st, 2004. Analogously to **Study I**, the cancer survivors were defined as having survived at least 5 years from initial cancer diagnosis without a second malignancy in this time period. Furthermore, the cancer survivors were divided into two groups by age at cancer diagnosis: below 20 years and between 20 and 34 years.

Study III: Cardiovascular medication after cancer at a young age in Finland: A nationwide registry linkage study.

In **Study III**, a total of 8,197 early onset cancer patients was included who had been diagnosed with a first malignancy from January 1st, 1993, until December 31st, 2004. In both **Study III and IV**, the 5-year cancer survival was not an obligatory inclusion criterion, as we investigated the drug purchases from the date of cancer diagnosis onwards. A total of 29,974 siblings served as reference group in Study III.

Study IV: Health conditions associated with metabolic syndrome after cancer at a young age: A nationwide register-based study.

In **Study IV**, a total of 7,551 subjects made up the early onset cancer patient cohort having received a primary cancer diagnosis between January 1st, 1994, until December 31st, 2004. The sibling cohort comprised 12,455 subjects.

4.3   METHODS

4.3.1 Retrieval of information on outcomes

Data on vital status

Information on the life status (death date, if applicable) and possible emigration of patients and siblings was available via the PRC.

Data on the outcomes

Patient and sibling outcomes

In **Studies I-IV**, the cancer patients/survivors were grouped by age at cancer diagnosis: childhood and adolescent patients (0-19 years) and young adult (YA) patients (20-34 years). This division took account of the similar diagnosis distribution and treatment regimens in those two major age groups. Thus, it allowed for a better comparison with previous data particularly on childhood cancer survivors.

The event-free 5-year survival is generally considered as a criterion for cancer survival. Since the cancer survivors' outcomes were investigated in **Study I and II**, the follow-up for healthy siblings started at the age of 5 years or 25 years, respectively. In **Study III and IV**, the follow-up started from cancer diagnosis to investigate any possible impact of cancer and cancer treatment on the purchases of cardiovascular medication or medication associated with metabolic syndrome. Hence, the follow-up of siblings started from birth or from the age of 20 years to have a comparable age range.

Study I

To identify hospitalizations in both the cancer survivor and sibling cohort, the subjects were linked to the HDR files. The observed cardiovascular outcomes in **Study I** included cardiomyopathy, cardiac insufficiency, myocardial infarction, cardiac ischemia, cardiac arrhythmia, atherosclerosis, and brain vascular thrombosis. For statistical analysis, information on outcomes with common etiologies were combined in order to avoid an overestimation of events, if the patient had both in the same category as follows: cardiomyopathy/ cardiac insufficiency, atherosclerosis/ brain vascular thrombosis, myocardial infarction/ cardiac ischemia, and cardiac arrhythmia. The follow-up ended at the date of hospitalization for any of the mentioned outcomes. Siblings with a cancer diagnosis after the age of 34 years were excluded from the cohort.

Study II

In this investigation, we compared causes of death in early onset cancer survivors to those of siblings and the general population. Statistics Finland reports causes of death in the general population grouped by specific classes. These causes of death (and the corresponding ICD-10 codes) were investigated in **Study II**: malignant causes, including primary and secondary malignancy (C00-D48), infectious and parasitic diseases (A00- B99, J65: pneumoconiosis with tuberculosis, cardiac and respiratory infections were regarded as cardiac and respiratory disease codes), all cardiovascular causes (I00-I42.5, I42.7-I99), cardiac ischemia-related conditions (I20- I25), respiratory diseases (J00-64, J66-J99), alcohol related causes (A00-R99, X45), diabetes (E10-E14), and suicide (X60-84, Y87.2).

To further analyze the number of deaths due to particular cardiovascular complications analogous to those investigated in **Study I**, we additionally assessed deaths due to these causes: cardiac ischemia/ myocardial infarction, cardiomyopathy/ cardiac insufficiency, atherosclerosis/ brain vascular thrombosis, other cardiac diseases, respiratory diseases, diabetes, external, and other causes.

Study III

First purchases of cardiovascular medications were analyzed with respect to the following ATC-categories as presented in Table 5.

Table 5: Subcategories of cardiovascular medications by ATC-code.

ATC-code	Medication
C01A	Cardiac glycosides
C01B	Antiarrhythmics, class I and III
C01D	Vasodilators used in cardiac diseases
C02	Antihypertensives
C03	Diuretics
C07	Beta blocking agents
C08	Calcium channel blockers
C09	Agents acting on the renin-angiotensin system
B01	Antithrombotic agents

Study IV

To assess the first purchases of medication associated with metabolic syndrome, we selected the following drugs as described in Table 6.

Table 6: Subcategories of medications associated with metabolic syndrome by ATC-code.

ATC-code	Medication
C02,C03, C07, C08, C09	Antihypertensives
A10A	Blood-glucose lowering drugs
A10B	Insulin
A10A, A10B	Any diabetes medication
C10	Lipid-lowering drugs

4.4   STATISTICAL ANALYSES

Study I and II

Cox proportional hazard models were assessed for adverse health events and causes of death. Calendar age was a time variable in calculating hazard ratios of the adverse events from **Study I**. Furthermore, cancer, birth decade, gender and the interaction between gender and cancer served as predictor variables. Additionally, the treatment era (1975-1982, 1983-1992, 1993-2004) was included as a predictor.

In Study II, we adjusted for birth decade and gender and the treatment era was a predictor (1960-1979, 1980-1989, and 1990-1999) for the HR analysis. To calculate HRs of additional categories of causes of death not offered by Statistics Finland, we selected particular health conditions as death causes as described earlier in this section.

Furthermore**,** standardized mortality ratios (SMRs) and 95% confidence intervals (CI) were computed with respect to causes of death reported by Statistics Finland. We selected the following categories of causes of death which were coded as International Classification of Diseases (ICD) codes: cancer-related (primary or secondary malignancy), infectious and parasitic diseases, all cardiovascular diseases, cardiac ischemia, respiratory causes, alcohol-related causes, diabetes, and suicide. Data on deaths and age-standardized mortality rates were available from 1971 until 2011.

The cumulative incidence plot of the selected adverse events and causes of death (**Study I and II**) were analyzed for two major groups: cancer survivors aged 0-19 years and those aged 20-34 years at diagnosis, and the sibling groups aged from 5 years and 25 years of age at the start of follow-up, respectively. **Study I** adjusted for gender and **study II** considered other causes of death as competing risk. Moreover, the cumulative

mortality was described with respect to the treatment era (prior to 1980, 1980-89, 1990-1999, and all periods combined).

Study III and IV

The hazard ratios for the first purchase of the respective drugs were analyzed in early onset cancer patients compared with the sibling cohort. The follow-up started from January 1st, 1993 (**Study III**) and 1994 (**Study IV**) until at the latest December 31st, 2011. In **Study IV**, the follow-up started at the earliest 1 year after cancer diagnosis to ensure that the cancer patients had not purchased the particular drugs prior to being diagnosed with cancer. Thus, we aimed to evaluate the purchases of drugs associated with metabolic syndrome as possible effect of cancer therapy. Death or a secondary malignancy (primary in siblings) were considered as competing risks. The follow-up of cancer patients or siblings ended prematurely in the case of death, a primary/ secondary malignancy, or emigration. Furthermore, HRs for the first drug purchase were evaluated by specific cancer diagnosis and age at diagnosis compared with siblings. In the **Study III and IV**, the HR analysis was computed via the Fine and Gray proportional subdistribution hazards method, which was adjusted for the birth year and age at the start of follow-up (Fine et al. 1999).

The cumulative incidence plots in the **Studies III and IV** of purchasing at least one of the drugs in the particular categories was computed from cancer diagnosis in early onset cancer patients and from the start of follow-up (birth or the age of 20 years) in siblings. Death or secondary (primary in siblings) malignancy were regarded as competing risks. The follow-up ended prematurely in the case of death, a secondary (or primary in siblings) cancer, or emigration. Statistical analyses were computed with SAS for windows version 9.3.

4.5   ETHICS

The study protocol for **Studies I-IV** was approved by the ethical committee of the South-West Finland Hospital District Review Board (ATMK 103/ 180/ 2011 (20.9.2011; 275). Permits for registry linkage were granted by the Finnish Ministry of Social Affairs and Health, the PRC, and Statistics Finland (THL/ 1184/5.05.00/2011).

5 RESULTS

5.1 CARDIOVASCULAR LATE ADVERSE HEALTH CONDITIONS AFTER EARLY ONSET CANCER

5.1.1 Analysis of cardiovascular morbidity by linkage to the hospital discharge register

In our initial study (Study I), the focus was set on cardiovascular morbidity after early onset cancer in comparison to siblings. Thus, we analyzed the hazard ratios (HRs) for cardiovascular complications in early onset cancer survivors compared to the sibling cohort (Table 7). Regarding all selected cardiovascular outcomes, the HRs were elevated in both childhood and young adult cancer survivors compared to siblings (Table 7). Highest HRs were found for both childhood (HR 13.5, 95%CI 8.9-20.5) and young adult (HR 3.6, 95% CI 2.8-4.6) cancer survivors for cardiomyopathy/ cardiac insufficiency. Those HR values were followed by a higher likelihood for developing atherosclerosis/ brain vascular thrombosis and myocardial infarction/ cardiac ischemia after childhood (HR 3.4, 95% CI 2.3-5.1 and HR 3.3, 95% CI 1.7-6.5) and young adult cancer (HR 1.7, 95%CI 1.4-2.0 and HR 1.8, 95% CI 1.5-2.1) in comparison to siblings (Table 7).

Table 7: Hazard ratio (HR), 95% confidence interval (CI) and number (N) of childhood, young adult (YA) cancer survivors and the overall early onset cancer survivor group for the respective cardiovascular outcomes compared to siblings. Bold: The highest HR values for developing the particular cardiovascular outcomes. (Modified from Study I).

	Childhood cancer		YA cancer		Early onset cancer	
Cardiovascular complication	**N**	**HR (95%CI)**	**N**	**HR (95%CI)**	**N**	**HR (95%CI)**
Cardiomyopathy/ Cardiac insufficiency	41	**13.5** (8.9-20.5)	107	3.6 (2.8-4.6)	148	4.6 (3.6-5.8)
Atherosclerosis/ brain vascular thrombosis	34	**3.4** (2.3-5.1)	176	1.7 (1.4-2.0)	210	1.8 (1.6-2.2)
Myocardial infarction/ cardiac ischemia	15	**3.3** (1.7-6.5)	205	1.8 (1.5-2.1)	220	1.8 (1.5-2.2)
Cardiac arrhythmia	30	**1.7** (1.2-2.6)	163	1.4 (1.2-1.7)	193	1.4 (1.2-1.7)

Since certain cancer diagnoses require treatments with possibly cardiotoxic agents, we investigated the likelihood of cardiovascular adverse effects by primary cancer diagnosis and age at diagnosis (Table 8). Among childhood cancer survivors, highest HRs for cardiomyopathy/ cardiac insufficiency were reported after malignant bone tumors (HR 24.0, 95% CI 10.6-54.6) and ALL (HR 18.4, 95% CI 4.5-17.4). Childhood bone cancer survivors were also most likely to experience atherosclerosis/ brain vascular thrombosis (HR 6.5, 95% CI 2.1-20.2). After childhood ALL and HL, the next highest

HR values were reported for this outcome compared with siblings. Moreover, childhood HL survivors were most prone to develop myocardial infarction/ cardiac ischemia (HR 14.6, 95% CI 7.5-28.5) among selected diagnosis groups compared to siblings.

In young adult cancer survivors, ALL survivors stood out with the most elevated HR (37.8, 95% 14.0-102) for developing cardiomyopathy/ cardiac insufficiency. Young adult brain tumor survivors showed the greatest HR values for suffering from atherosclerosis/ brain vascular thrombosis (HR 4.9, 95% CI 3.6-6.8). The highest HR values for myocardial infarction/ cardiac ischemia were observed for both childhood and YA HL survivors (HR 14.6, 95%CI 7.6-28.5 and HR 8.0, 95% CI 6.4-10.1, respectively) compared to siblings (Table 8). In contrast to that, childhood and YA melanoma and thyroid cancer survivors showed the same risk for developing cardiovascular disease as the sibling cohort.

Therapies of childhood and young adult cancer have undergone changes, since the negative adverse effects have become apparent. Thus, efforts have been made to reduce toxicities and late complications. We analyzed the cumulative incidence of the particular cardiovascular late effects by attained age, treatment era (1975-1989 and after 1990) and age at cancer diagnosis (below 20 years or between 20 and 34 years at diagnosis) to search for any differences between the treatment periods (Figure 7). The cumulative incidence of cardiomyopathy/ cardiac insufficiency was reduced to 2% from 4% approaching the age of 40 years among childhood cancer survivors towards the most recent treatment era. In contrast, the cumulative incidence for this effect seemed similar among young adult cancer survivors until a rising tendency was visible after 50 years of age for those having been treated in the earliest treatment period. Furthermore, the cumulative incidence for atherosclerosis/ brain vascular thrombosis seemed higher after childhood and young adult cancer in the latest treatment era. Furthermore, the cumulative incidence for myocardial infarction/ cardiac ischemia seemed rather similar among the respective treatment periods. Interestingly, the cumulative incidence of cardiac arrhythmia appeared higher in both age groups that had been treated in the latter era.

Table 8: Hazard ratio (HR) and 95% confidence interval (CI) for the respective cardiovascular outcomes by cancer diagnosis and age at cancer diagnosis compared to siblings. The bolded values are markedly elevated HRs. (Modified from Study I).

Diagnosis	Cardiomyopathy/ cardiac insufficiency		Atherosclerosis/brain vascular thrombosis		Myocardial infarction/ Cardiac ischemia		Cardiac arrhythmia	
	0-19y HR (95% CI)	20-34y HR (95%CI)	0-19y HR (95% CI)	20-34y HR (95% CI)	0-19y HR (95% CI)	20-34y HR (95%CI)	0-19y HR (95% CI)	20-34y HR (95% CI)
AML	**18.4** (4.5-74.4)	4.4 (0.6-31.3)	0	1.4 (0.2-10.3)	**10.5** (1.5-74.9)	0	5.0 (0.7-35.4)	1.2 (0.2-8.8)
ALL	**6.6** (3.0-14.2)	**37.8** (14.0-102)	**5.1** (2.4-10.9)	3.5 (0.5-24.6)	1.8 (0.3-13.2)	0	**3.3** (1.3-8.0)	0
HL	**14.8** (7.2-30.4)	**13.3** (9.5-18.7)	**5.0** (2.1-12.2)	**3.2** (2.2-4.6)	**14.6** (7.5-28.5)	**8.0** (6.4-10.1)	**4.9** (2.2-11.1)	**3.5** (2.5-4.9)
NHL	**13.4** (5.5-32.8)	**8.4** (4.9-14.5)	3.4 (0.8-13.7)	**2.2** (1.2-4.0)	0	1.6 (0.8-3.0)	**7.2** (3.0-17.6)	**2.4** (1.4-4.1)
CNS	1.5 (0.4-6.3)	1.4 (0.5-3.7)	**4.8** (2.6-9.1)	**4.9** (3.6-6.8)	0.8 (0.1-5.6)	1.4 (0.8-2.3)	0.8 (0.2-3.2)	1.0 (0.5-1.9)
Renal	**16.0** (5.9-43.9)	0	3.2 (0.5-23.1)	2.5 (0.8-7.6)	0	1.2 (0.3-4.7)	**9.0** (2.9-28.2)	0.7 (0.1-4.8)
Bone	**24.0** (10.6-54.6)	1.7 (0.2-12.4)	**6.5** (2.1-20.2)	1.7 (0.6-5.4)	3.0 (0.4-21.7)	0.9 (0.2-3.8)	0	1.0 (0.3-4.1)
Soft tissue	0	0.8 (0.2-3.1)	1.4 (0.2-9.7)	1.0 (0.5-2.0)	2.1 (0.3-14.7)	0.8 (0.4-1.6)	2.3 (0.6-9.2)	0.9 (0.5-1.8)
Thyroid	0	0.9 (0.4-2.2)	0	1.2 (0.8-1.9)	0	0.5 (0.2-0.9)	0	1.1 (0.7-1.7)
Melanoma	0	1.1 (0.5-2.7)	0	0.8 (0.4-1.5)	0	0.8 (0.5-1.4)	1.9 (0.3-13.5)	1.0 (0.7-1.8)
Colon	3.7 (0.5-26.6)	1.0 (0.2-4.0)	3.9 (1.0-15.5)	0.7 (0.3-1.8)	0	0.8 (0.4-1.8)	1.5 (0.2-10.9)	1.2 (0.6-2.4)
Breast	**140.4** (19.5-1010)	1.8 (0.9-3.6)	0	0.6 (0.3-1.2)	0	0.9 (0.5-1.5)	0	1.1 (0.7-1.8)
Testicular	6.2 (0.9-44.0)	**3.2** (1.6-6.4)	**3.3** (0.5-23.8)	1.6 (0.9-1.9)	0	1.6 (1.0-2.7)	2.7 (0.4-19.5)	**1.9** (1.2-3.2)

A

B

C
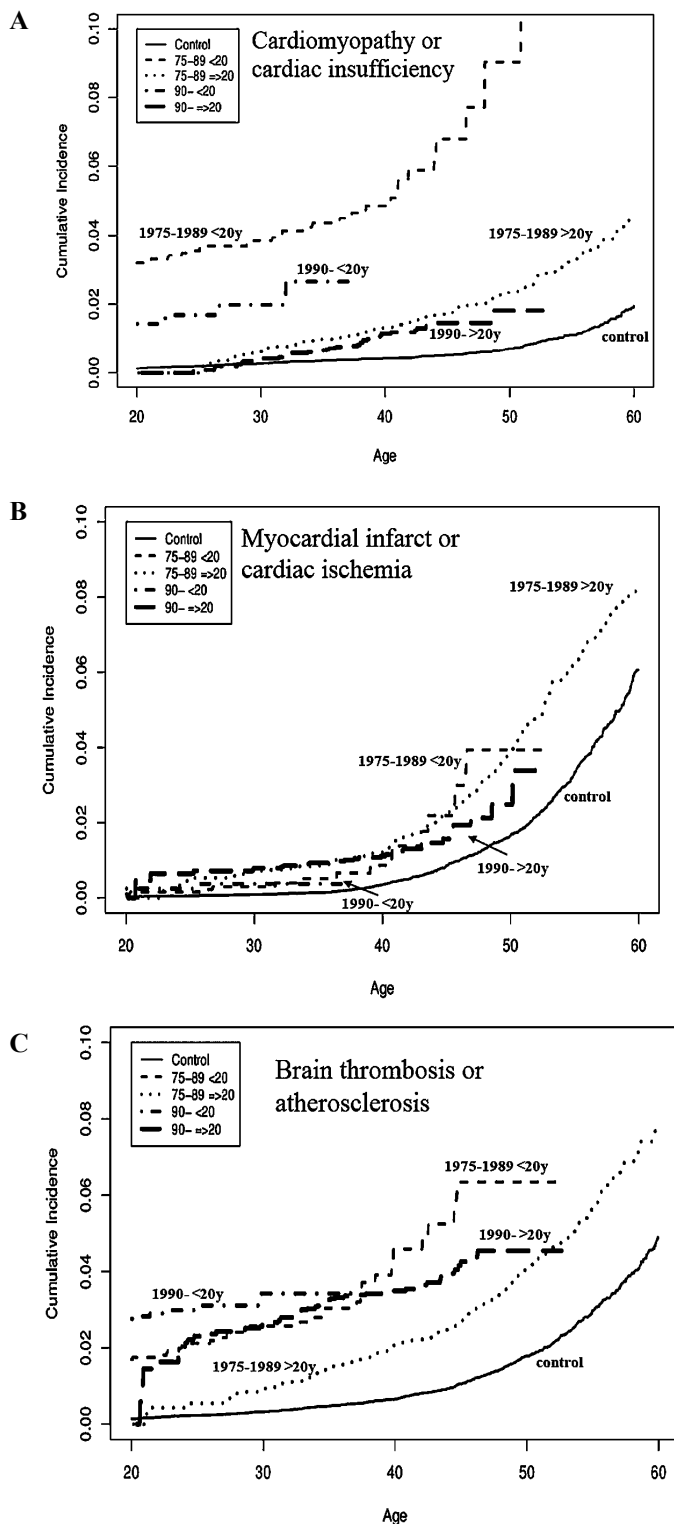
Figure 7: Cumulative incidence of the respective cardiovascular morbidities by treatment era in early onset cancer survivors and siblings and attained age (years) (cancer survivors were subdivided into 2 groups: below 20years (<20y) and 20-34years (>20y) at cancer diagnosis). The respective treatment eras were: 1975-1989 and after 1990. A) cardiomyopathy/ cardiac insufficiency, B) myocardial infarction/ cardiac ischemia, and C) brain thrombosis/ atherosclerosis.

5.1.2 Analysis of cardiovascular morbidity by linkage to the drug purchase register

After analyzing the cardiovascular morbidity via diagnoses from the HDR, we were interested in the purchases of cardiovascular medication and drugs associated with the metS. This offered novel insights into cardiovascular treatments on an out-patient basis. The HR for purchasing any cardiovascular medication were elevated after both childhood and YA cancer compared to siblings (HR 7.2, 95% CI 5.1-10.1 and HR1.7, 95% CI 1.5-1.9). The likelihood for the purchase of anticoagulants was also increased for both patient groups, especially after childhood cancer (HR 19.8, 95% CI 8.5-45.9 versus HR 2.5, 95%CI 2.0-3.2 after YA cancer) (Figure 8).
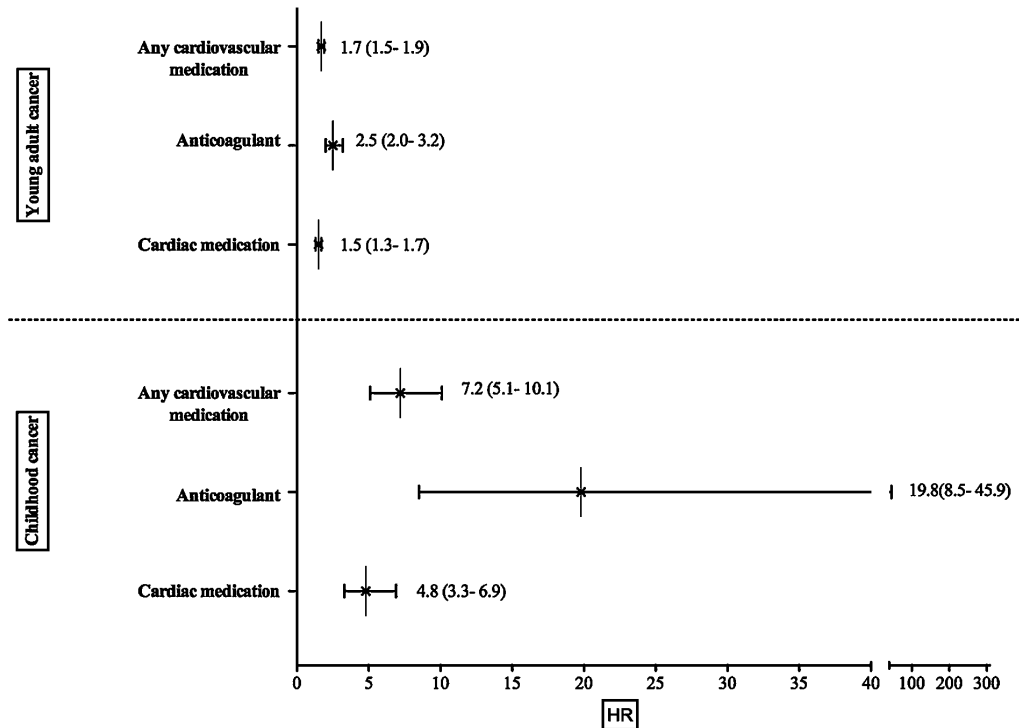
Figure 8: Hazard ratios and 95% confidence intervals for the first purchase of cardiovascular medication in childhood and young adult cancer patients compared to siblings

Since the category of cardiac medication comprises a large variety of different drug classes, we investigated the purchases of the subcategories of these drugs. Concerning cardiac drugs, the highest values were found for renin-angiotensin inhibitors (HR 17.3, 95% CI 4.1-72.8) and Calcium channel-blockers (HR 12.6, 95% CI 3.8-41.9) after childhood cancer. Moreover, YA cancer patients were most prone to buy cardiac glycosides (HR 39.3, 95% CI 5.0-308.9), diuretics (HR 4.4, 95% CI 3.3-5.9) and calcium channel blockers (HR 1.7, 95% CI 1.2-2.4) compared to siblings (Table 9). In general, HR values for purchasing cardiovascular medication were more elevated after childhood cancer with the exception of purchasing cardiac glycosides after YA cancer.

Table 9: Hazard ratios (HRs) and 95% confidence intervals (CI) for purchasing cardiovascular drugs in childhood and YA cancer patients compared to siblings by drug class. Dark grey: the only non-significantly elevated HRs in this table. (Modified from Study III).

Drug	HR (95%CI) Childhood cancer	HR (95%CI) YA cancer
Any cardiac medication	4.8 (3.3-6.9)	1.5 (1.3-1.7)
Cardiac glycoside	9.6 (2.6-35.8)	39.3 (5.0-308.9)
Diuretic	8.3 (3.3-21.1)	4.4 (3.3-5.9)
Betablocker	3.1 (2.0-4.7)	1.2 (1.0-1.4)
Ca-channel-blocker	12.6 (3.8-41.9)	1.7 (1.2-2.4)
Renin-Angiotensin-system-inhibitor	17.3 (4.1-72.8)	1.3 (1.0-1.7)

As the metabolic syndrome is a major risk factor for developing cardiovascular disease, we analyzed the purchase of medications targeting traits of the metS after early onset cancer compared with siblings (Figure 9). With respect to antihypertensives and diabetes medication, increased HR values for their purchase were found after both childhood and YA cancer in comparison to siblings (HR 4.6, 95% CI 3.1-7.0 and HR 3.0, 95% CI 1.5-6.1 in childhood and HR 1.5, 95% CI 1.3-1.8 and HR1.6, 95% CI 1.1-2.2 in YA cancer patients). Concerning the subclasses of diabetes medications, opposite trends were visible in childhood and YA cancer patients, but HR values remained nevertheless elevated compared to siblings for both cancer patient groups. While childhood cancer patients were more prone to purchase blood-glucose lowering drugs (HR 5.7, 95% CI 1.5-21.1) than insulins (HR 2.7, 95% CI 1.1-6.2), YA cancer patients were more likely to purchase only insulins (HR 2.6, 95% CI 1.5-4.4). Moreover, elevated HRs were found for the purchase of lipid-lowering drugs in both patient groups, but this did not reach significance.
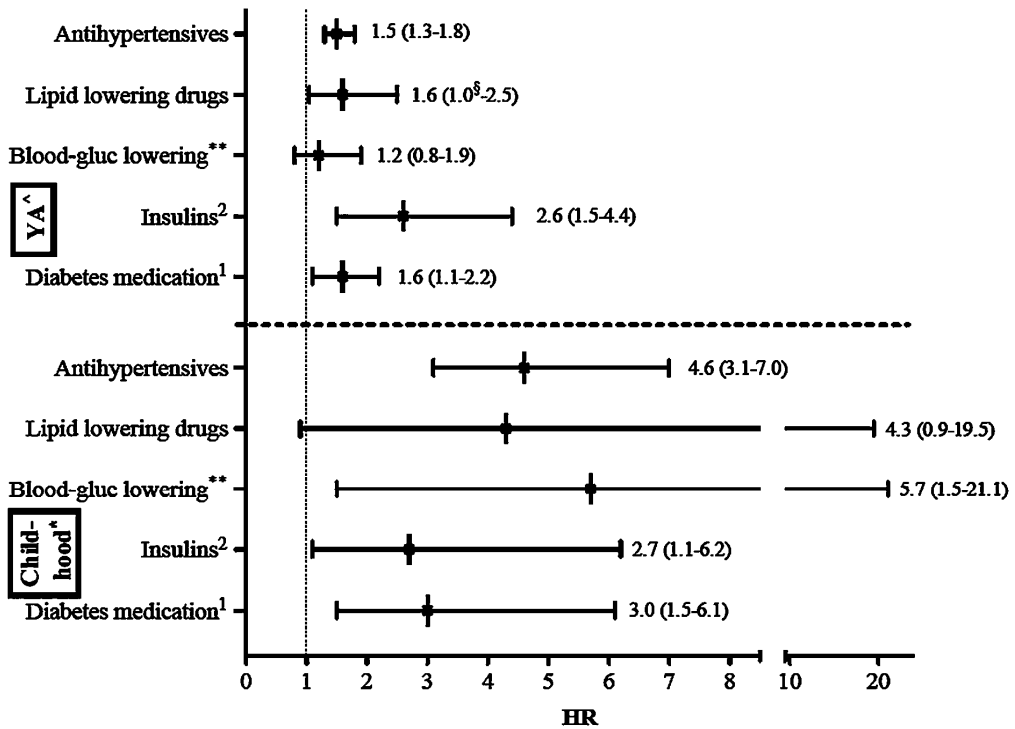
Figure 9: Hazard ratios and 95% confidence intervals for purchasing medication associated with the metS after childhood and young adult (YA) cancer compared to siblings. Any diabetes medication including insulins and blood-glucose lowering drugs. (Modified from Study IV).

Furthermore, we compared the purchases of antihypertensives within the specific cancer diagnosis groups to those of siblings (Figure 10). Childhood ALL, malignant bone tumor and neuroblastoma patients showed the highest likelihood of purchasing antihypertensives compared to siblings. While most of the childhood cancer diagnosis groups were associated with elevated HRs for purchasing antihypertensives, only YA ALL and AML showed an increased HR value for purchasing this drug class compared to siblings.
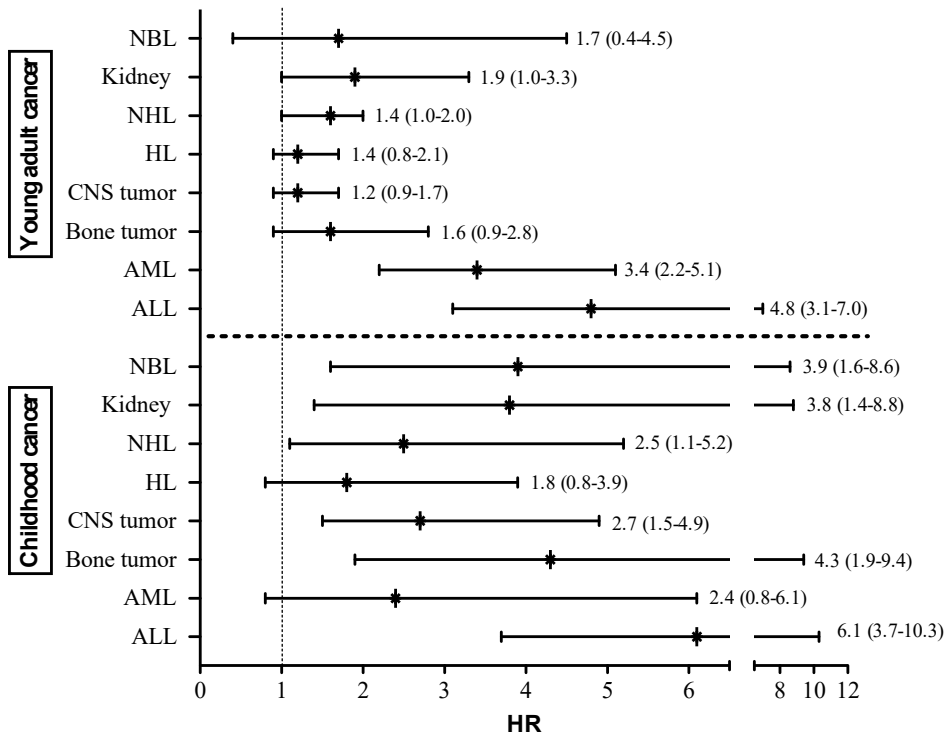
Figure 10: Hazard ratios (HRs) and 95% confidence intervals for purchasing antihypertensives after childhood and YA cancer by diagnosis. ALL: Acute Lymphoblastic Leukemia, AML: Acute Myeloid Leukemia, CNS: Central Nervous System. HL: Hodgkin lymphoma. NHL: Non Hodgkin lymphoma. NBL: Neuroblastoma.

Concerning the purchases of diabetes medication, elevated HR values were only observed after early onset ALL, AML and CNS tumors (Figure 11). Increased HR figures in both age groups of the same cancer diagnosis were only found in childhood and YA ALL patients (HR 6.3, 95% CI 2.7-14.8 in childhood and HR 3.7, 95% 1.2-9.4in YA ALL patients). Moreover, childhood AML and CNS tumor patients were more likely to purchase this drug class than siblings (HR 7.6, 95% CI 1.9-24.5 and HR 3.5, 95% 1.3-9.2). Regarding the purchase of lipid-lowering drugs, an elevated HR value was found only after childhood ALL (data not shown/shown in the original article IV).
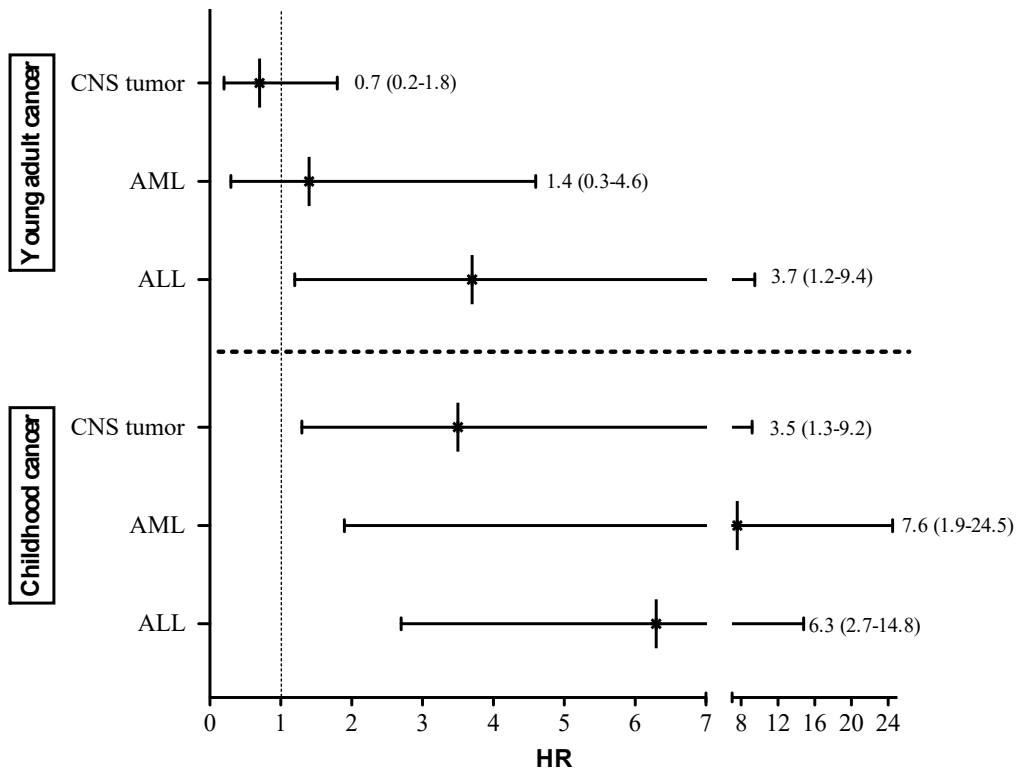
Figure 11: Hazard ratios (HRs) and 95% CI (confidence intervals) for purchasing diabetes medication in childhood and young adult (YA) cancer patients by diagnosis. ALL: Acute Lymphoblastic Leukemia, AML: Acute Myeloid Leukemia, CNS tumor: Central Nervous System tumor. (Modified from Study IV).

The cumulative incidences of purchasing antihypertensives and diabetes medication showed an increasing tendency over time for all investigated groups (Figure 12A-C). However, the cumulative incidence curves for these purchases in childhood and YA cancer patients were in a higher range especially at the end of the follow-up. Greatest differences between both cancer patient groups and the respective sibling cohorts were noticed for antihypertensives (Figure 12A). At the end of follow-up, 2% of childhood cancer and 8% of YA cancer patients had purchased these drugs compared to almost none in the younger sibling and 2% in the older sibling group. Divergent trends were also visible concerning diabetes drugs and lipid-lowering drugs (Figure 12B and C).
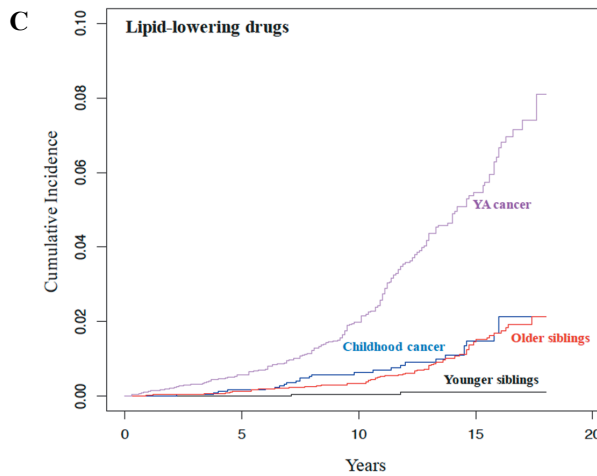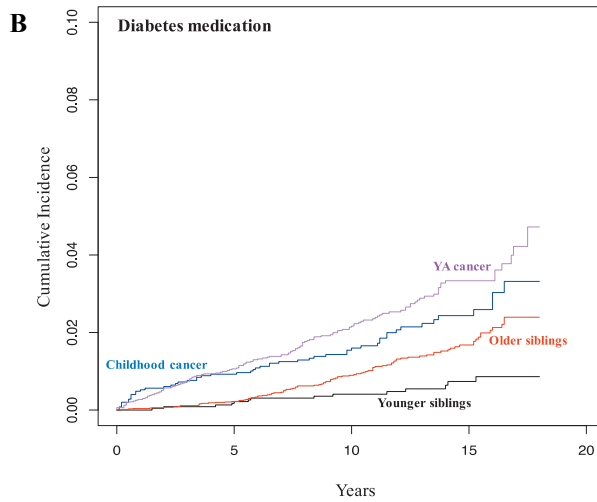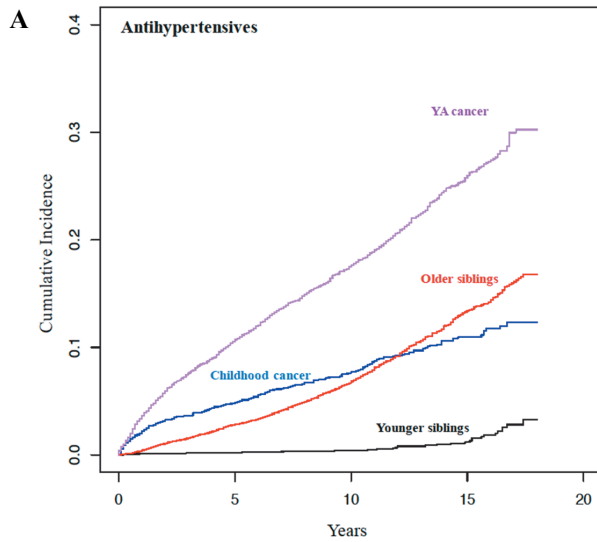
Figure 12: Cumulative incidence of purchasing A) antihypertensives, B) diabetes medication and C) lipid-lowering drugs by time from cancer diagnosis/ the start of follow-up (years) Blue: childhood and pink: young adult (YA) cancer patients. Black: younger and red: older siblings.

5.2   CAUSE-SPECIFIC AND CARDIOVASCULAR MORTALITY AFTER EARLY ONSET CANCER

In Study II, the focus was set on the overall mortality and cardiovascular mortality in a total of 16,769 5-year survivors of early onset cancer. The overall standardized mortality rates (SMRs) in both childhood and young adult cancer survivors were elevated compared with the general population (SMR 7.6, 95% CI 7.0-8.2 and SMR 4.2, 95% CI 4.0-4.3) (Table 10). Cancer-related death accounted for the highest SMRs in both age groups (SMR 37.6, 95%CI 34.1-41.1 and SMR 10.9, 95% CI 10.4-11.2). Among the non-malignant causes of death, infectious and parasitic diseases were associated with the highest SMR figures, but nonetheless rather low case numbers. Cardiovascular causes of death lead to the next highest SMRs in both groups of cancer survivors (SMR 4.3, 95% CI 3.0-5.6 and SMR 1.7, 95% CI 1.5-2.0). Moreover, the SMR for other causes of death were increased in cancer survivors compared with the general population (SMR 4.3, 95% 3.0-5.6 and SMR 1.7, 95% 1.5-2.0). The overall SMR in siblings was comparable to that of the general population. Interestingly, the SMR for cardiac ischemia was slightly lower than the general population (SMR 0.8, 95% CI 0.7-0.9). In contrast, the SMRs for death from cardiac ischemia were elevated after childhood (SMR 5.3, 95% CI 2.9-7.7) and YA (SMR 1.8, 95% CI 1.5-2.1) cancer. Only in young adult cancer survivors, an increased SMR value was found regarding respiratory diseases (SMR1.7, 95% CI 1.1-2.4) (Table 10).

Table 10: Standardized mortality ratios (SMRs) and 95% confidence intervals (CIs) for causes of death in childhood and young adult cancer survivors and siblings.[1] Infectious and parasitic diseases.[2] Cardiac ischemia/ myocardial infarction.[3] Overall deaths due to cardiovascular causes. O/E: Observed/ Expected. Bold: Markedly elevated HR values. (Modified from Study II).

Cause of death	Cancer survivors				Siblings	
	Aged 0-19 years at diagnosis		Aged 20-34 years at diagnosis			
	O/E	SMR (95%CI)	O/E	SMR (95%CI)	O/E	SMR (95% CI)
Cancer	455/12	**37.6** (34.1-41.1)	1699/156	**10.9** (10.4-11.2)	435/501	0.9 (0.8-1.0)
Infectious[1]	7/1	**10.0** (2.6-17.4)	17/4	**4.0** (2.1-5.8)	18/21	0.9 (0.5-1.3)
Cardiac ischemia[2]	19/4	**5.3** (2.9-7.7)	127/72	**1.8** (1.5-2.1)	209/256	**0.8** (0.7-0.9)
All cardiovascular diseases[3]	41/10	**4.3** (3.0-5.6)	228/133	**1.7** (1.5-2.0)	418/487	0.9 (0.8-1.0)
Respiratory diseases	2/1.4	NA	29/17	**1.7** (1.1-2.4)	66/63	1.0 (0.8-1.3)
External	21/18	1.2 (0.7-1.7)	45/55	0.8 (0.6-1.1)	358/409	0.9 (0.8-1.0)
Other	55/12	**4.8** (3.5-6.1)	136/59	**2.3** (1.9-2.7)	479/289	**1.7** (1.5-1.8)
Overall	615/81	**7.6** (7.0-8.2)	2274/547	**4.2** (4.0-4.3)	2436/2458	1.0 (1.0-1.0)

Since the cancer treatment has changed from the initiation of systematic cancer treatment, the hazard ratios for the respective cardiovascular causes of death were investigated according to the treatment era (Table 11). Infectious and parasitic diseases as causes of death accounted for the highest HR figures in the earliest treatment era from 1966 until 1979 and then decreased towards the most recent era. In contrast, the HR to die from cardiomyopathy/ cardiac insufficiency and respiratory conditions was highest in the treatment period from 1980-1989 (HR 3.4, 95% CI 1.7-7.1 and HR 2.2, 95% CI 1.2-4.3) compared to siblings. Concerning both particular causes of death, the HR values declined towards the more recent era from 1990-1999, showing no increased risk for death from the investigated causes in comparison to siblings. When looking at all eras taken together, all cardiovascular causes of death showed were twice as likely in early onset cancer survivors than in siblings.

Table 11: Hazard ratios (HRs) and 95% confidence intervals (CIs) for causes of death by treatment era among early onset cancer survivors compared to the sibling cohort [1]Infectious and parasitic diseases. Bold: Markedly increased HR values.

Cause of death	Treatment era							
	All combined		1966-1979		1980-1989		1990- 1999	
	HR	95%CI	HR	95%CI	HR	95%CI	HR	95%CI
Infectious[1]	**5.8**	**3.0-11.1**	**8.7**	**4.1-18.5**	**4.5**	**1.7-11.7**	2.1	0.4-10.0
Cardiac ischemia/ myocardial infarction	**2.6**	**2.1-3.2**	**2.6**	**2.0-3.8**	**2.7**	**1.9-3.8**	2.1	1.0-4.4
Cardiomyopathy/ cardiac insufficiency	**2.5**	**1.4-4.3**	2.2	1.0-4.8	**3.4**	**1.7-7.1**	1.3	0.3-7.1
Arteriosclerosis/ brain vascular thrombosis	**2.3**	**1.5-3.7**	**2.4**	**1.4-4.2**	**2.5**	**1.1-5.6**	1.4	0.3-6.5
Respiratory disease	1.6	1.0-2.4	1.4	0.8-2.4	**2.2**	**1.2-4.3**	0.8	0.1-5.9
External causes	**1.7**	**1.4-2.0**	**2.0**	**1.6-2.6**	**1.8**	**1.4-2.4**	1.2	0.9-1.7

As cardiovascular morbidity was different according to the primary cancer diagnosis, the SMRs were analyzed according to the selected cancer diagnosis groups and causes of death (Table 12). In all selected diagnosis categories of early onset cancer survivors, the overall SMR were more elevated than in the general population. The overall SMR values ranged from a likelihood to die from 1.8-times in early onset testicular cancer survivors to 12.6-times in early onset ALL survivors (SMR 12.6, 95% CI 10.3-15.0). Furthermore, early onset CNS tumor (SMR 11.9, 95% CI 11.0-12.8) survivors were associated with the next highest SMR values overall. Both early onset ALL (SMR 101.0, 95% CI 81.3-120.0) and CNS (SMR 44.4, 95% CI 40.8-48.0) survivors were most prone to death from cancer compared to the general population. Early onset HL survivors stood out with highest SMR figures due to cardiac ischemia (SMR 8.0, 95% CI 6.0-8.0) and any cardiovascular disease (SMR 5.4, 95% CI 4.2-6.6). After early onset CNS tumors and HL, respiratory diseases were 5.7- and 5.9-more likely as causes of death than in the general population. Interestingly, suicide was rather a cause of death in early onset NHL survivors than in the general population (SMR 2.9, 95% CI 1.3-4.6).

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Table 12: SMRs among early onset cancer survivors according to cancer diagnosis and cause of death (O/E= observed/ expected, CI= confidence interval). ALL: Acute Lymphoblastic Leukemia. AML: Acute Myeloid Leukemia. CNS: Central Nervous System-tumor. HL: Hodgkin Lymphoma, NHL: Non-HL. NA: Not Applicable. [1] Infectious and parasitic disease. [2] Cardiac ischemia/ myocardial infarction. [3] Any cardiovascular condition. Bold: Markedly elevated HR values. (Modified from Study II).

Cause of death	ALL O/E	ALL SMR 95%CI	CNS O/E	CNS SMR 95%CI	HL O/E	HL SMR 95%CI	NHL O/E	NHL SMR 95%CI	Bone tumors O/E	Bone tumors SMR 95%CI	Breast cancer O/E	Breast cancer SMR 95%CI	Testicular cancer O/E	Testicular cancer SMR 95%CI
Overall	115 / 9	**12.6** 10.3-15	715 / 60	**11.9** 11-12.8	420 / 61	**6.9** 6.2-7.5	146 / 32	**4.6** 3.8-5.3	64 / 22	**2.9** 2.2-3.6	370 / 50	**7.4** 6.6-8.1	105 / 58	**1.8** 1.5-2.1
Cancer	101 / 1	**101.0** 81.3-120	582 / 13	**101.0** 40.8-48	285 / 14	**21.0** 18.5-23.4	86 / 7	**12.8** 10.1-15.5	41 / 5	**8.2** 5.7-10.7	334 / 18	**18.9** 16.8-20.9	41 / 10.5	**3.9** 2.7-5.1
Infectious disease[1]	1 / 0.1	NA	6 / 0.5	**12.0** 2.4-21.6	9 / 0.5	**18.0** 6.2-29.8	0 / 0.2	NA	0 / 0.1	NA	1 / 0.4	NA	1 / 0.4	NA
Cardiac ischemia[2]	1 / 0.2	NA	12 / 5.9	2.0 0.9-3.2	61 / 7.6	**8.0** 6.0-10	14 / 4	**3.5** 1.7-5.3	5.0 / 3	1.7 0.2-3.1	10 / 3.8	2.6 1.0-4.2	14 / 9.4	1.5 0.7-2.3
Any Cardiovasc.[3]	3 / 0.7	NA	35 / 11.7	**3.0** 2-4.0	75 / 13.9	**5.4** 4.2-6.6	27 / 7	**3.7** 2.3-5.1	7 / 5.4	1.3 0.3-2.3	17 / 9	1.9 1.0-2.8	23 / 15.6	1.5 0.9-2.1
Respiratory disease	0 / 0.1	NA	8 / 1.4	**5.7** 1.8-9.7	10 / 1.7	**5.9** 2.2-9.5	4 / 0.9	4.4 0.1-8.8	0 / 0.6	NA	0 / 1.4	NA	0 / 1.7	NA

In both childhood and YA cancer survivors, cardiovascular cumulative mortality prevailed among the non-malignant causes of death at the end of follow-up. In YA cancer survivors, cardiovascular cumulative mortality markedly dominated as the non-malignant cause of death already after 15 years from the start of follow-up (Figure 13A).
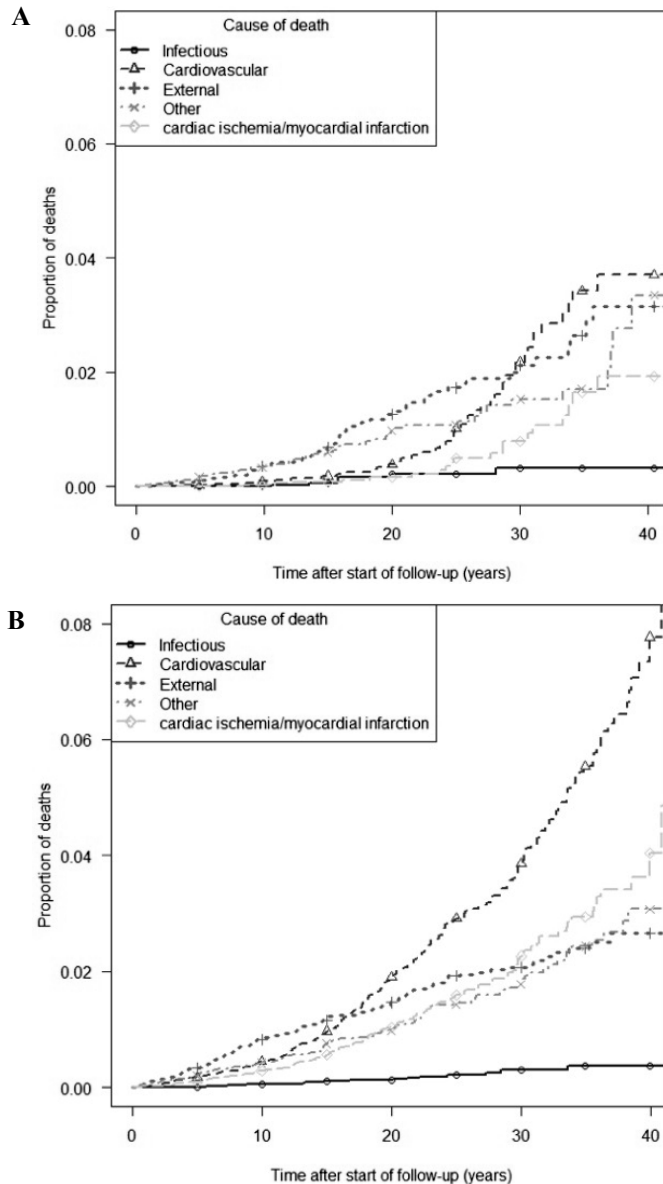
Figure 13: Cumulative non-malignant mortality in A) childhood and B) young adult (YA) cancer survivors by the cause of death and time from the start of follow-up (5-year cancer survival).

In addition to cardiac complications, other non-malignant causes of death were observed in a lower range around 3% at the end of follow-up. Contrasting this, cardiovascular cumulative mortality in childhood cancer survivors emerged as the leading reason for death much later around 35 years from follow-up (Figure 13B).

Furthermore, we investigated the cumulative cardiovascular mortality in childhood and YA cancer survivors by diagnosis type (Figure 14A-C). The highest cardiovascular cumulative mortality was observed after both childhood and YA HL (Figure 14A, B). In childhood HL survivors, the cumulative mortality reached about 11% at the end of follow-up. The remaining selected diagnosis groups were associated with a cumulative cardiovascular mortality around 4% by the end of follow-up (Figure 14A). After YA Hodgkin lymphoma, the highest cardiovascular cumulative mortality was found at the end of follow-up approaching 15% (Figure 14B). The next highest trends were visible for YA malignant bone tumor and CNS tumor survivors reaching about 8% at the end of follow-up. While cumulative mortality due to cardiovascular causes was more elevated in testicular cancer survivors than after breast cancer, the values approached 8% for both groups after 35 years from follow-up, but the high divergent increase at the end was most likely due to few cases that were possible to follow for this long time period (Figure 14C).
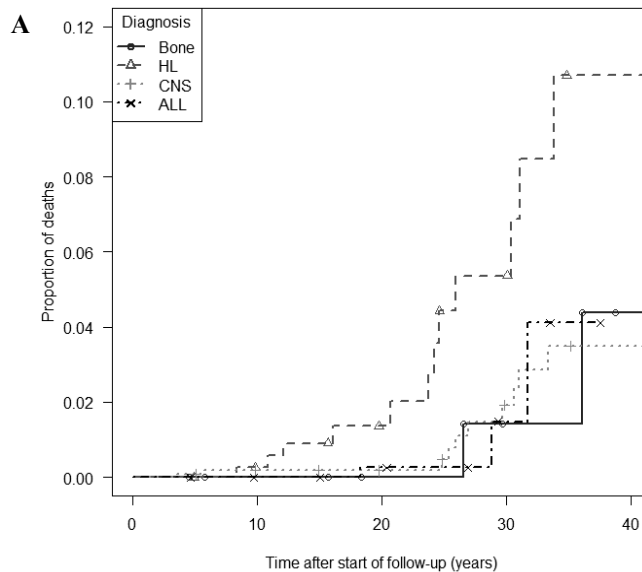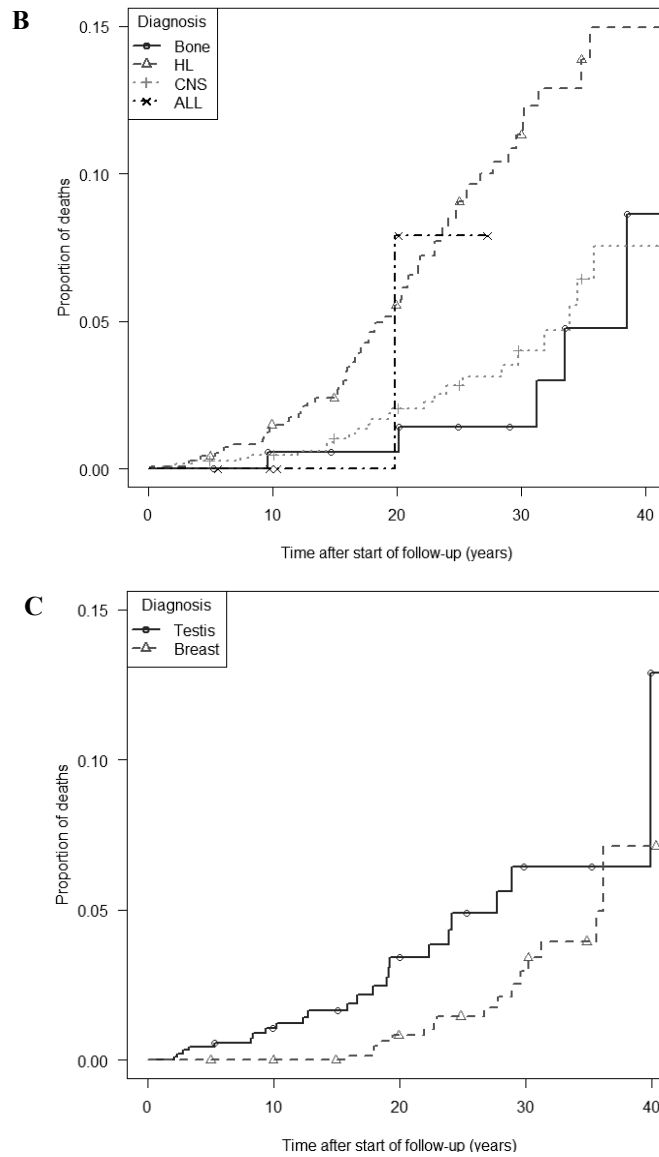
Figure 14: Cumulative mortality due to cardiovascular diseases in childhood and YA cancer survivors by cancer diagnosis and age at diagnosis: A) childhood malignant bone tumor, HL, CNS tumor, and ALL survivors, B) young adult malignant bone tumor, HL, CNS tumor, and ALL survivors, and C) YA breast and testicular cancer survivors.

6   DISCUSSION

6.1   LATE ADVERSE CARDIOVASCULAR EFFECTS AFTER EARLY ONSET CANCER

The main goal of this thesis was to evaluate the cardiovascular morbidity and mortality after cancer at a young age in comparison to healthy siblings and the general population. We were able to shed new light on the cardiovascular health burden after both childhood and YA cancer in a nationwide setting. This thesis was based on data from health care registries with an exceptionally long-follow-up of up to 45 years from cancer diagnosis (maximally 33 years and, concerning morbidity and drug purchases, 18 years). Our data on late effects and mortality particularly after young adult cancer offered valuable novel insights into this specific cancer survivor population. Studies III and IV were the first to present a nationwide overview of cardiovascular drug purchases after childhood and YA cancer.

Thus far, a large body of literature has dealt with late morbidity in childhood cancer survivors (Oeffinger et al. 2006, Geenen et al. 2007, Kenney et al. 2010, Hudson et al. 2013, Armstrong et al. 2014). While secondary cancer is the most feared health condition after childhood cancer, cardiovascular late effects have emerged as the major non-malignant complications (Kremer et al. 2001, Lipshultz et al. 2005, Mulrooney et al. 2009, Castellino et al. 2011, van der Pal et al. 2012, Armstrong et al. 2013, Gudmundsdottir et al. 2015). Prior research has extensively reviewed late effects after childhood cancer and demonstrated an increased risk for late adverse health conditions compared to the general population and sibling cohorts. In contrast, this topic has rather recently been addressed in YA cancer survivors (Aleman et al. 2007, van Laar et al. 2014, Zhang et al. 2014). Only few follow-up studies in childhood and YA cancer survivors stand out with very long follow-up times (Robertson et al. 1994, Garwicz et al, 2012, Armstrong et al. 2016). Consequently, our investigations with a maximal follow-up time of 45 years offers pivotal new information on the very late cardiovascular effects after cancer at an early age.

Taken together, we demonstrated that both childhood and YA cancer survivors were more likely to suffer from cardiovascular complications than their siblings. In our first study on cardiovascular morbidity, childhood cancer survivors were associated with greater HR figures for all investigated cardiovascular outcomes than YA cancer survivors. Among the cardiovascular late effects, the highest HR values were recorded for cardiomyopathy/ cardiac insufficiency in both childhood and YA cancer survivors. There was a 13-fold risk of this cardiac effect among childhood cancer survivors compared to siblings; among YA cancer survivors the risk was 3.6-fold. The HR values for atherosclerosis/ brain vascular thrombosis and myocardial infarction/ cardiac ischemia were elevated in both childhood and YA cancer survivors compared to siblings, yet markedly lower than for cardiomyopathy (SMR 3.4/ SMR 1.8 and SMR

3.5/SMR 1.7, respectively). The HR values for cardiac insufficiency/ cardiomyopathy were higher compared to those in a previous childhood cancer survivors study, while the HR values for myocardial infarction were lower (Mulrooney et al. 2009). These differences could be partially explained by the divergent approaches of data retrieval: self-reporting by childhood cancer survivors in the CCSS report and linkage to the HDR in our analysis. Additionally, the diagnosis of congestive heart failure may not comprise as many diagnoses compared to the broader choice in study I consisting of both cardiac insufficiency and cardiomyopathy (Mulrooney et al. 2009).

We addressed the effect of time from the initial cancer diagnosis and treatment by analyzing the cumulative incidences of specific cardiovascular adverse outcomes. In study I, the cumulative incidence for cardiomyopathy/ cardiac insufficiency was distinctly higher in early onset cancer survivors than in siblings and the trend was increasing over time with no visible plateau throughout the follow-up. Eventually, its cumulative incidence approached 4% and 5% at the end of our follow-up in childhood and YA cancer survivors, respectively. The steadily increasing cumulative incidence of cardiomyopathy mirrored reports stating that the time span from treatment with anthracycline to clinical heart failure may range from close to anthracycline treatment to up to many decades after exposure (Kremer et al. 2002 B, van Dalen et al. 2006, Sieswerda et al. 2012). Since the data from studies I, III and IV required cardiovascular symptoms that either led to a registered hospital discharge diagnosis or to a registered purchase of cardiac medication, the cardiovascular outcomes in this thesis may be underestimated rather than overestimated. This underestimation holds true for both cancer survivors and siblings. Asymptomatic cardiovascular disease among childhood cancer survivors may be present in up to 57% of the childhood cancer population (Kremer et al. 2002 A). It is known that the risk for anthracycline-induced cardiac heart failure is dose dependent (especially at doses above 250–300mg/m^2), this cardiac condition may occur after the exposure to much lower doses of anthracycline (above 45mg/m^2) (Lipshultz et al. 1995, Kremer et al. 2002, van Dalen et al. 2006, Mulrooney et al. 2009, Chow et al. 2015).

The wide range of the time of onset of symptoms and the divergent impact of radiation and drug exposure doses underscore the multifactorial etiology of cardiac insufficiency. Life-long regular cardiac check-ups after administration of anthracycline is pivotal to decrease the burden of this potentially lethal disease (Lipshultz et al. 1995, Oeffinger et al. 2006, van Dalen et al. 2006, Armenian et al. 2015). A prediction model for assessing the likelihood of heart failure after childhood cancer therapy has been proposed for detection of this potentially fatal condition in early, asymptomatic, stages. The dose-dependent risk for anthracycline cardiotoxicity was demonstrated in a Dutch study, which showed that the cumulative incidence of cardiac insufficiency nearly doubled after 20 years from chemotherapy, if the anthracycline dose exceeded 300mg/m^2 (van Dalen et al. 2006). Taken together, several key risk factors for the development of cardiac insufficiency have been identified, such as the anthracycline dose, exposure to radiation therapy, female gender, and age at cancer diagnosis (Chow et al. 2015). These

factors also explain the varying cardiovascular morbidity and mortality figures by initial cancer diagnosis in this thesis.

In study I, the cumulative incidence of all particular cardiac outcomes was higher in childhood and YA cancer survivors compared to the corresponding sibling cohorts. This is in concordance with the findings from the CCSS concerning the younger age group in our report (Mulrooney et al. 2009). The most diverging trends of cumulative incidence between childhood cancer and YA cancer survivors and the sibling cohorts was recorded for cardiomyopathy/ cardiac insufficiency, which is an indication of the higher likelihood of developing these sequelae after cancer therapy than siblings. This was confirmed by the highest observed HRs for cardiomyopathy/ cardiac insufficiency in both childhood and young adult cancer survivors compared to siblings in study I. These results are in line with a study among childhood cancer survivors (Mulrooney et al. 2009). The median age of onset of congestive failure was lower in childhood cancer survivors than their siblings and its occurrence was higher (Mulrooney et al. 2009). Furthermore, the age range of this cardiac condition among childhood cancer survivors was strikingly broad, from 7 to 50 years in the followed patient cohort compared to a later age at diagnosis and a narrower range in siblings (Mulrooney et al. 2009).

The cumulative incidence of cardiomyopathy/ cardiac insufficiency decreased to half from 4% to 2% in childhood cancer survivors that had received cancer therapy after 1990 compared to the earlier treatment periods (study I). In contrast to that, the cumulative incidence for cardiomyopathy was similar regardless of the treatment periods after YA cancer, reaching 1% at an attained age of 40 years. Furthermore, the cumulative incidence of myocardial infarction approached 1% at the attained age of 40 years in childhood and YA cancer survivors (study I). These results resembled previous findings. Mulrooney and colleagues investigated the cardiac outcomes after cancer treatment between 1970 and 1986 in childhood cancer survivors (CCSS) (Mulrooney et al. 2009). At 30 years of follow-up the cumulative incidence of cardiac insufficiency was 4%, which is in line with our findings from the earlier treatment era. The results on the cumulative incidence of myocardial infarction were in the same range as ours.

In study 1, most childhood cancer diagnosis groups were at a higher risk for cardiomyopathy/ cardiac insufficiency compared to siblings. A larger study of childhood cancer survivors in the Nordic countries was in agreement with this finding (Gudmundsdottir et al. 2015). Since particular cancer diagnoses require specific treatment regimens concerning chemotherapy and/or irradiation, the burden of chronic late effects varied by cancer diagnosis (Oeffinger et al. 2006, Geenen et al. 2007, Tukenova et al. 2010, Lipshultz et al. 2012, Lipshultz et al. 2013 B).

The diagnosis-specific results in study I reveal that particular childhood cancer diagnosis groups, such as ALL, AML, NHL, HL, and malignant bone tumors, are associated with an elevated risk for cardiomyopathy/ cardiac insufficiency. These diagnosis groups were very likely to be exposed to anthracyclines and also to irradiation during their cancer treatment, which placed them at higher risk for cardiovascular

complications as previously reported (Oeffinger et al. 2006, Geenen et al. 2007, Tukenova et al. 2010, Lipshultz et al. 2012, Lipshultz et al. 2013 B). Of the diagnosis-specific cardiac morbidity, Wilms' tumor patients exhibit a rising cumulative frequency of congestive heart failure. In the study of Green et al the cumulative incidence by 20 years after the primary diagnosis and exposure to anthracyclines was 4.4% (Green et al. 2001). The impact of the cancer diagnosis and its resulting therapy play an important role in the risk stratification of cancer survivors and this has to be considered when adequate cardiovascular follow-up guidelines are planned by international experts (Kremer et al. 2013, Armenian et al. 2015).

The age range at cancer diagnosis in the patient cohorts in studies I-IV spanned up to the age of 34 years and this offers new insights into the YA age category which has been underrepresented in studies up to date (Michelagnoli et al. 2003). Previous investigations on late effects after young adult cancer have reported variable age ranges at cancer diagnosis as an inclusion criterion: below 28 years (Adams et al. 2004), between 15 and 29 years (van Laar et al. 2014), and between 20 and 24 years at cancer diagnosis (Zhang et al. 2014). This hampers the comparison with other studies on young adult cancer patients.

In study I, we report a markedly increased risk of cardiomyopathy/ cardiac insufficiency after both childhood and YA HL. Childhood HL survivors are at an increased risk for cardiac insufficiency due to their cancer treatment (mediastinal irradiation and anthracyclines) (Mulrooney et al. 2009, Gudmundsdottir et al. 2015). A recent investigation stated that childhood cancer survivors aged below 14 years were more likely to become hospitalized due to various cardiac conditions, *e.g.*, pericardial disease or cardiomyopathy, and heart failure, than older survivors aged 14–29 years at cancer diagnosis (van Laar et al. 2014). Both age groups of survivors were nevertheless at a higher risk for cardiac disease than the general population (van Laar et al. 2014). Van Laar and colleagues inspected the hospital admissions due to cardiac diagnoses via registry linkage, but their patient cohort was regional and not nationwide as the cohorts in this thesis. A study from all Nordic countries offered insights into the risk for hospital admission due cardiovascular disease in childhood cancer survivors (Gudmundsdottir et al. 2015). The risk was highest for cardiomyopathy (RR 9.9, 95% CI 8.0-12.1) and their other results were in concordance with ours as well and confirmed our findings in childhood cancer survivors (Gudmundsdottir et al. 2015). The risk for admission due to cardiac failure was also elevated in the same childhood cancer diagnosis groups, which is in line with our results, namely acute leukemia, lymphoma, malignant bone tumor, and renal tumor survivors (Gudmundsdottir et al. 2015). Childhood ALL, AML, and Wilms' tumor survivors have also been reported to develop cardiac complications, which is in line with our results (Green et al. 2001, Gudmundsdottir et al. 2015). Childhood malignant bone tumor survivors are the most likely ones to experience morbidities among patients with childhood cancer (Hudson et al. 2003, Geenen et al. 2007). This observation is of exceptional impact, since childhood bone tumor patients were associated with the highest HR values for both cardiomyopathy/ cardiac

insufficiency and myocardial infarction/ cardiac ischemia in our report (Study I). This finding mirrored what is known about treatment-associated late cardiovascular complications from before, since childhood bone tumor patients receive anthracyclines during their cancer therapy.

We found a significantly elevated risk for atherosclerosis/ brain vascular thrombosis in childhood and young adult ALL, HL, CNS tumor, malignant bone tumor, and young adult NHL survivors, which is in line with previous observations (Bowers et al. 2005, Bowers et al 2006, Aleman et al. 2007). Cranial radiotherapy has been identified as a risk factor for stroke, especially when it exceeds 30 Gray (Bowers et al. 2006) and supradiaphragmatic radiation has been associated with stroke in childhood cancer survivors (van Dijk et al. 2016). Cranial radiation therapy may lead to stroke in two ways: first it induces a (non-atherosclerotic) vasculopathy and then it may lead to intracranial atherosclerosis, adding to the risk for stroke (Mueller et al. 2013). This pathomechanism explains the underlying risk for stroke in those cancer diagnosis groups where with this type of irradiation is used for therapy. Hypertension, and in particular the combination of diabetes mellitus and hypertension, are known risk factors for stroke in childhood cancer survivors (Mueller et al. 2013). In a study of adult HL survivors younger than 60 years at diagnosis, de Bruin and colleagues revealed that the major mechanisms leading up to stroke were large-artery atherosclerosis and cardioembolisms (De Bruin et al. 2009). They also pointed out that cardiovascular conditions, such as hypertension, diabetes mellitus, and hypercholesterolemia, amplify the risk for stroke in this cancer survivor population (De Bruin et al. 2009).

In concordance with the elevated risk for diabetes mellitus after childhood cancer, we revealed an increased likelihood of purchasing drugs for diabetes mellitus after both childhood and YA cancer (Talvensaari et al. 1996, Neville et al. 2006, Majhail et al. 2009, Holmqvist et al. 2014). While some of the studies on the metS/diabetes have offered crucial new information on individual laboratory tests and features of metabolic syndrome in childhood cancer survivors, the sizes of the study populations have been limited (Talvensaari et al. 1996, Neville et al. 2006, Taskinen et al. 2007). Other investigations have relied on self-reported outcomes of risk factors for metS, which carries a risk for recall bias (Meacham et al. 2010, Smith et al. 2014).

The exposure to cranial and abdominal irradiation has been shown to predispose for diabetes mellitus, obesity, and the metabolic syndrome (Tonorezos et al. 2015). These forms of treatment are often applied in CNS tumor, ALL, and HL patients and thus, the traits of metabolic syndrome occur more commonly in these patient groups (Tonorezos et al. 2015). Cranial radiation may disrupt the hypothalamic-pituitary axis, which, in turn, promotes the development of metabolic disturbances, if left untreated (Crowne et al. 2015). Childhood sarcoma and testicular cancer survivors are also at risk of metabolic pathologies (Nuver et al. 2005, Hoffman et al. 2008). Other clinical symptoms associated with the metS, such as dyslipidemia, hypertension, and hyperinsulinemia, may occur in childhood cancer survivors (Talvensaari et al. 1996, Taskinen et al. 2000, Pietila et al. 2009, Siviero-Miachon et al. 2008, Nottage et al. 2014).

Total body irradiation used as pretreatment for allogeneic hematopoietic stem cell transplantation is a strong risk factor for the metS (Taskinen et al. 2000, Taskinen et al. 2007, Meacham et al. 2010, Armenian et al. 2012). A study from the Nordic countries pointed out that pediatric Wilms' tumor, leukemia, CNS tumor, germ-cell malignancies, malignant bone tumors, and HL survivors were at highest risk for diabetes mellitus among all childhood cancer survivors (Holmqvist et al. 2014). In their cancer survivor population, diabetes mellitus type 2 was more common than type 1 (Holmqvist et al. 2014). In childhood, diabetes mellitus type 1 usually prevails (Craig et al. 2014). Due to damage to the pancreatic cells and a decrease in the release of insulin as a consequence of cancer therapy (irradiation and asparaginase chemotherapy), a new definition for diabetes mellitus after cancer treatment has been proposed (de Vathaire et al. 2012). Our results underline the risk of this type of diabetes, as the hazard ratio for the purchase of blood-glucose lowering drugs other than insulins was higher (HR 5.7) than that for insulins (HR 3.0) in childhood cancer survivors. A significantly increased risk for the use of antihypertensives, lipid-lowering drugs, and diabetes medication has also been reported previously among childhood cancer survivors compared to siblings (OR 1.9, 1.7, and 1.6) (Meacham et al. 2010). Our findings in childhood cancer survivors were in agreement, since we found an increased likelihood of purchasing antihypertensives and diabetes medication in childhood cancer survivors compared to siblings, while the hazard ratios for lipid-lowering drugs were not significant. This discrepancy may be due to differences between the recall methods of questionnaires and registry data, as well as due to the larger cohort size of childhood cancer survivors in the mentioned CCSS study (Meacham et al. 2010). Our findings on lipid-lowering drugs might have become significant, had our cohort size been larger. Of note, Meacham and colleagues did not specify the precise drug classes, but rather described the broad medication categories (Meacham et al. 2010). In contrast, we analyzed the purchase of cardiovascular drugs by subcategory. No information was available on the use of anticoagulants comparable to our descriptions.

Rather recently, the focus of research has extended from childhood cancer to adverse health events in young adult cancer survivors older than 20 or 21 years at cancer diagnosis (Madanat et al. 2008 B, Prasad et al. 2012, van Laar et al. 2014, Gunn et al. 2015, Chao et al. 2016). The selected age ranges at cancer diagnosis in previous investigations have varied as follows: 15–39 years, 16–24 years, 20–34 years, and 20–24 years. We chose the two major age ranges of below 20 years and 20–34 years at cancer diagnosis to enable the comparison of the results after childhood cancer with other large international childhood cancer survivor studies. Only few studies have offered insights into late adverse effects the age range of 20–34 years at cancer diagnosis chosen for this thesis, which focuses specifically on YA cancer survivors (Prasad et al. 2012, Ahomaki et al. 2015). Some studies were regional or institutional and others nation-wide and applied different methods of the data retrieval. These differences in age ranges must be kept in mind when comparing our observations after YA cancer to those of other investigations.

6.2   OVERALL AND CARDIOVASCULAR MORTALITY AFTER EARLY ONSET CANCER

The survival after childhood cancer has been overshadowed by reports on long-term excess mortality following cancer therapy. Numerous studies have focused on this topic and the overall SMR values after childhood cancer ranged from SMR 8.3 to 17.2 (Mertens et al. 2001, Cardous-Ubbink et al. 2004, Mertens et al. 2008, Reulen et al. 2010, Tukenova et al. 2010, Garwicz et al. 2012, Armstrong et al. 2016). This variation may be due to methodological differences, such as different cut-off ages at cancer diagnosis, geography, follow-up time, size and set-up of the cancer survivor cohort, and the form of data retrieval and documentation of the mortality data. It has been recognized that the cumulative mortality due to the recurrence of the malignancy zeniths at 9 years after childhood cancer and then declines after 15 years (Cardous-Ubbink et al. 2004, Armstrong et al. 2009). Since the main focus of this thesis was set on non-malignant, particularly cardiovascular mortality, the deaths from primary and secondary malignancies were combined into one category in study II.

Cancer-related causes of death stood out with the highest SMR figures in study II. In line with our findings, deaths due to cancer have previously been demonstrated as the leading cause of death (Robertson et al. 1994, Mertens et al. 2001, Cardous-Ubbink et al. 2004, Mertens et al. 2008, Armstrong et al. 2009, Reulen et al. 2010, Garwicz et al. 2012). Among the non-malignant causes of death, we found that cardiovascular causes accounted for the second highest SMR values. In study II, the highest SMR value resulted from infectious and parasitic diseases, but this cause of death accounted for only a small number of death. When interpreting the data via SMR analysis, it is critical to remember that the causes of death in the general population serve as a reference. Thus, rather common cardiovascular causes of death in the general population used in the denominator of the SMR-values affected the results differently than for infectious diseases that are less common causes of death. We demonstrated a steep increase of cardiovascular cumulative mortality at 15 and 25 years from cancer diagnosis among YA and childhood cancer survivors in study II. Among the non-malignant causes of death, cardiovascular conditions have stood out in previous childhood cancer survivor studies, as well (Mertens et al. 2008, Armstrong et al. 2009, Reulen et al. 2010, Tukenova et al. 2010). A mortality report from the CCSS demonstrated that non-malignant, non-external causes of death exceeded the risk for death from cancer recurrence after 30 years from the cancer diagnosis, stressing that negative cardiovascular outcomes may become apparent only decades after cancer treatment (Armstrong et al. 2009). With respect to cardiovascular causes of death, elevated risks have been associated with the administration of >360mg/m^2 of anthracyclines and a mediastinal radiation dose of more than 5 Gray in childhood cancer survivors (Tukenova et al. 2010), but we were not able to present precise data on the medical cancer treatment.

Analogously to our findings on childhood cancer survivors, we demonstrated that cancer was the dominant cause of death in YA cancer survivors (study II). This finding is in

concordance with prior reports on mortality after YA cancer (Prasad et al. 2012, Zhang et al. 2012). Prasad and colleagues analyzed cause-specific mortality in childhood and YA cancer survivors (Prasad et al. 2012) and reported similar findings as in study II: the SMRs for both malignant and non-malignant complications were higher among childhood cancer survivors than YA cancer survivors. However, the childhood cancer survivors had been grouped differently by Prasad and colleagues by age at cancer diagnosis: younger than 14 years and between 15 and 19 years at cancer diagnosis (Prasad et al. 2012). This difference and the lack of results on all cancer survivors combined below the age of 20 years at diagnosis hampers a direct comparison to our findings. Furthermore, study II compared the mortality ratios to a healthy sibling cohort in addition to presenting SMRs with respect to the general population. While the time of cancer diagnosis ranged from 1966 to 1999 in Prasad's investigation, study II extended the time range from 1966 to 2004 (Prasad et al. 2012).The overall SMR rose from the 1970s to a higher SMR figure in 1990 to 1995 (Zhang et al. 2012), but overall mortality after childhood cancer declined towards the more recent treatment era in study II which was consistent with earlier findings (Armstrong et al. 2010, Garwicz et al. 2012, Armstrong et al. 2016).

Our observations from study II on cause-specific mortality in childhood cancer survivors are in line with other studies, since we found the highest overall mortality rates after childhood ALL and CNS tumors (Mertens et al. 2001, Reulen et al. 2010, Armstrong et al. 2016). Regarding YA cancer survivors, we observed the highest SMR values after YA CNS tumors and HL, which is also in line with a previous investigation (Prasad et al. 2012). In a study on testicular cancer survivors, death from circulatory disease was more likely among those having received their diagnosis younger than 35 years (Fossa et al. 2007). Among HL lymphoma survivors aged 15 to 24 years at cancer diagnosis, the overall SMR for those older than 20 years at HL diagnosis was higher than of younger patients (Bhuller et al. 2016). In study II, a lower SMR due to cardiovascular disease was reported for HL survivors aged 20 to 34 years at diagnosis than for survivors younger than 20 years at cancer diagnosis. However, the two age groups were differently defined and this choice may have accounted for the diverging SMR trends. A large Dutch institution-based study on 5-year survivors of HL lymphoma followed up survivors for maximally 40 years (van Nimwegen et al. 2015). Although the age range at cancer diagnosis was broad and included patients aged up to 50 years at cancer diagnosis, the study it offered new insights into the cardiovascular health status in the following age categories: below 18 years, 18–24 years, 25–29 years, and 30–39 years at cancer diagnosis. This allows for rather similar age set-as in study II (van Nimwegen et al. 2015). The standard incidence ratio (SIR) in their study was elevated due to cardiac failure/ insufficiency and coronary heart disease compared to the general population, more so for cardiac failure/ insufficiency. In agreement with the comparable HR findings in study II, the SIR figures were highest among HL cancer survivors younger than 18 years at cancer diagnosis and then steadily decreased, but remained elevated in comparison to the general population (van Nimwegen et al. 2015).

6.3 STRENGTHS AND LIMITATIONS

Long-term follow-up studies are pivotal for identifying the key risk factors and risk profiles related to the harmful effects of cancer treatment. Large, long-term studies can provide crucial data to improve individualized guidelines for the surveillance of early onset cancer survivors. The largest studies by the CCSS have been institution-based and they have often relied on information obtained by self-reported questionnaires (Robison et al. 2002). The draw-back for this form of data retrieval is a risk of recall bias. The diagnosis spectrum of the CCSS excluded retinoblastoma (a separate research had been undertaken on this group) and other rare childhood cancer tumors, such a hepatoblastoma and germ cell tumors (Robison et al. 2002). Other large patient cohorts, such as that from the Nordic countries, have so far only focused on childhood cancer survivors younger than 20 years at diagnosis (Garwicz et al. 2012, Gudmundsdottir et al. 2015). To date, only few investigations have been carried out with subjects up to 34 years at cancer diagnosis and including young adult cancer survivors older than 20 years at cancer diagnosis (Prasad et al. 2012).

This thesis reported the first nationwide studies on cardiovascular morbidity and cardiovascular medication via registry linkage after early onset cancer. So far, no previous study has accessed information from national drug purchase registries related to cancer patients with a similarly broad age range at cancer diagnosis (younger than 35 years). Previously, the CCSS has demonstrated a higher likelihood of using drugs for hypertension, dyslipidemia, or diabetes in childhood cancer survivors compared to siblings (Meacham et al. 2010). This conclusion was based on self-reporting and may not provide as accurate information as registry-based national drug purchase data (Furu et al. 2010, Meacham et al. 2010). The follow-up (study III and IV) on drug purchases of maximally 18 years allowed for a long-term ascertainment. To limit an overflow of data, the first purchase of drugs was selected as the outcome variable and any longer duration of medical treatment could not be verified. However, increased cardiovascular morbidity over time after childhood cancer has extensively been demonstrated earlier, confirming the chronic nature of this condition. Some intermittent cardiovascular drug therapy may occur, especially after hematopoietic stem cell transplantation (Majhail et al. 2009). In the patient cohort in studies III and IV, this form of therapy was administered only to a minority of patients. Furthermore, there was no access to laboratory test results nor information on body weight, smoking or other lifestyle habits, which would have strengthened the data. Therefore, it was not possible to assess any modifiable risk behavior in cancer survivors/ patients nor siblings in contrast to reports from the CCSS (Armstrong et al. 2013).

The results of study III and IV were based on linkage to the drug purchase registry, offering an overview of the cardiovascular morbidity also on an out-patient level after early onset cancer. With respect to cardiac medication, childhood cancer patients purchased renin-angiotensin inhibitors more likely than their siblings, but the highest likelihood for purchases was found for cardiac glycosides after YA cancer compared to

siblings. Since the diagnosis of cardiovascular diseases is usually made after symptoms and since the disease may be asymptomatic in its early stages, the purchases of cardiovascular medication probably underestimate the true cardiac morbidity in cancer patients and their siblings (Kremer et al. 2002 A). Additionally, the drug purchases only allowed for the assumption of certain treated illnesses, since there was no access to the specific diagnosis for the prescribed medication. Nevertheless, certain drug classes, such as cardiac glycosides, are strongly associated with particular diagnoses, such as heart failure (Hunt et al. 2009). The drug purchase served as a proxy for cardiovascular morbidity after early onset cancer as outpatients, but it must be acknowledged that it was not equivalent with cardiovascular diagnoses. Additionally, it was not possible to evaluate the drug compliance of the patients and siblings.

Again, the large cancer patient/ survivor cohorts in studies I-IV were not limited to a region or any institution, but data on a national level was retrieved via national registries. Nonetheless, a registry-based analysis has several drawbacks, and it was not possible to retrieve particular treatment information regarding any specific chemotherapy and/ or radiation therapy. On the other hand, the treatment regimens for the most common childhood cancer diagnosis groups follow international protocols (Schmiegelow et al. 2010).

A further limitation of this study was that individual laboratory values or diagnostic procedures were not available, in contrast to other reports (Talvensaari et al. 1996, Taskinen et al. 2000, Gurney et al. 2006, van der Pal et al. 2010, Lipshultz et al. 2012). Nevertheless, prior important investigations were consequently limited in size due to the individual assessment of outcomes (Gurney et al. 2006, Nottage et al. 2014).

In the mortality study (study II), general population data were assessed in addition to the healthy sibling cohort which served as a reference group in all four articles. The choice of a sibling cohort as a control may appear as a disadvantage at first sight, but at the same time it could be regarded as a strength of the studies I-IV. Especially in Finland, which may be considered as genetic isolate, regional differences in the genetic set-up have been identified in the context of diseases, such as familial hypercholesterolemia (Vuorio et al. 2001). As a consequence, the healthy sibling cohort most likely shares the equivalent genetic, socioeconomic, environmental, and behavioral background with subjects from the early onset cancer patient cohort. Therefore, a major distinguishing element between siblings and cancer patients was the administered cancer therapy. This allowed for a thorough evaluation of findings on the long-term impact of cancer and cancer treatment particularly on the cardiovascular system and mortality in general. Also other large international studies have selected siblings as a control for childhood cancer survivors (Robison et al. 2002, Kenney et al. 2010). Ideally, one could have chosen an age- and sex-matched sibling group, but it was not possible due to the restricted access to personal data. Instead, the analyses were adjusted for age and date of birth.

A strength of this thesis was the nationwide access of valid registry data on cancer patients, cardiovascular hospital discharge diagnoses, cardiovascular drug purchases,

and causes of death (Teppo et al. 1994, Furu et al. 2010). As a consequence, the current findings were neither subject to recall bias nor influenced by a preselection of study cohorts (Ness et al. 2009). The causes of death were assessed via death certificates that may not always have shown the accurate underlying and final cause of death, but this applies for other mortality studies as well and should not interfere with the comparison to previous results (Messite et al. 1996).

6.4   FUTURE ASPECTS TO REDUCE CARDIOVASCULAR LATE EFFECTS AFTER EARLY ONSET CANCER

To gain further insights into cardiovascular late adverse conditions, long-term studies of large cohorts with a detailed follow-up are imperative. Rather recently, young adult cancer survivors have received new attention with respect to late complications and it is important to continue to fill in the knowledge gap on late cardiovascular adverse effects in this group of cancer survivors. Cardiovascular complications after cancer therapy may be reduced and prevented by various approaches: modified lifestyle, changes in the cardiotoxic profile of cancer therapy, early detection and screening of cardiovascular sequelae, and timely and appropriate medication to treat adverse cardiac outcomes (Figure 15).

Modifiable health-related behavior, such as a healthy lifestyle, regular aerobic physical exercise, a balanced diet, and avoidance of tobacco and excessive alcohol will, when implemented, reduce the risk for cardiovascular complications (Armstrong et al. 2013, Smith et al. 2014, Akam-Venkata et al. 2016, Jarvela et al. 2016). Physical exercise may particularly improve cardiac function and help to maintain a healthy lifestyle (Jarvela et al. 2012, Jarvela et al. 2016). Additional prospective large studies are necessary to confirm the beneficial effect of physical exercise to reduce the impact of cardiotoxicity after cancer therapy. During follow-up care, health care professionals should inform cancer patients about their elevated cardiovascular risk after cancer therapy and stress the importance of adopting a healthy lifestyle to prevent cardiac adverse effects. The prevention of cardiac complications should be a cornerstone of the long-term cardiovascular follow-up of patients who have been treated for cancer at a young age.

Efforts have been also made to reduce the toxicity of cancer therapies. New effective chemotherapeutic drugs have been discovered, such as the bi-specific T cell engager (BiTe) antibodies, which couple cyctotoxic T cells to the tumor for subsequent eradication (Bachireddy et al. 2015). Blinatumomab is a promising agent of this novel drug category and has been approved for the treatment of relapsed Philadelphia chromosome-negative B-ALL (Bachireddy et al. 2015). In the future, blinatumomab may also be used to treat other B-cell malignancies, such as relapsed B-cell lymphoma. Additional BiTe antibodies with different targets are currently being investigated. Adoptive cellular therapy presents a novel type of cancer therapy. Here, tumor-specific T-cells are stimulated *ex vivo* and reintroduced to the host to promote tumor-specific T

cell-mediated killing of the tumor (Bachireddy et al. 2015). T cells with second-generation chimeric antigen receptors, CARs, have achieved remissions in two thirds of both pediatric and adult patients with relapsed ALL (Maude et al. 2014, Bachireddy et al. 2015).

Cardioprotective strategies have been suggested to reduce the cardiotoxicity of anthracyclines. As an example, a pegylated liposomal doxorubicin drug has been generated and claimed to be less cardiotoxic than conventional doxorubicin (Lipshultz et al. 2013 A). Since liposomal doxorubicin accumulates to a higher extent in the tumor milieu, drug levels are lower in the plasma and thus, this drug may cause less toxicity. Studies on its effect are still ongoing (Lipshultz et al. 2013 A). There is no evidence that continuous anthracycline infusion is superior to bolus administration despite initial claims for this effect (Lipshultz et al. 2013 A). The use of dexrazoxane for cardioprotection in childhood cancer therapies has remained controversial due to a fear of secondary malignancies (Akam-Venkata et al. 2016). Recent investigations have addressed this issue and confirmed that the treatment with dexrazoxane is not associated with an increased risk for malignancies (Schwartz et al. 2016). Dietary oxidants, such as vitamin A, C, E, coenzyme Q, and carnitine, might prevent anthracycline-induced cardiotoxicity, but this effect remains controversial (Lipshultz et al. 2013 A).

Due to different opinions and some unclear conclusions on cardiomyopathy screening guidelines, an international group of health professionals has formulated the cornerstones for long-term cardiovascular follow-up (Armenian et al. 2015). The international guideline harmonization group (IGHG) has issued valuable evidence-based guidelines for health care professional to ensure adequate cardiovascular screening and treatment (Armenian et al. 2015). Nevertheless, numerous guidelines and proposals have remained inconclusive. Hence, further research is needed to clarify their role in the surveillance of cancer survivors. The IGHG has agreed on echocardiography as the first-line screening modality after treatment with anthracyclines and/ or mediastinal radiation (Armenian et al. 2015). A recent study on cardiovascular late effects during and after adult cancer therapy has pointed out the necessity of regular echocardiograms even before the start of chemotherapy and during chemotherapy (Cardinale et al. 2015). While cardiac magnetic resonance imaging may be the most thorough method of cardiac screening, its high costs and limited availability prevent its regular use for screening (Lipshultz et al. 2013 A). The use of cardiac biomarkers, such as the natriuretic peptides (ANP, BNP, and the N-terminal pro-brain natriuretic peptide (NT-proBNP)) and the cardiac troponins T and I, have been discussed as screening tools for cardiomyopathy but require more research as screening tools (Dolci et al. 2008, Ylanen et al. 2015, Armenian et al. 2015). There are additional crucial open questions regarding cardiac screening and treatment: the impact of long-term follow-up for cardiac outcomes, medical interventional treatment, the prognostic value of biomarkers for cardiac dysfunction in asymptomatic patients, and the long-term effects of dexrazoxane (Armenian et al. 2015). Especially long-term follow-up studies beyond 30 years from the diagnosis with early onset cancer would be very valuable for the assessment of very

late effects, as additional information on the specific screening time-points after the exposure to cardiotoxic therapy is needed. Attempts have been made to establish an individualized screening program based on a risk-score after childhood cancer therapy (Chow et al. 2015). However, such a risk calculation does not take modifiable cardiovascular risk factors, such as hypertension and obesity into consideration, and requires further modifications to be fully functional as an assessment method for the health burden of cancer survivors (Chow et al. 2015).

Cardio-oncology is a recent subspecialty focusing on the professional assessment and a specialized therapy of treatment-related cardiotoxicity after cancer (Lenneman et al. 2016). It represents an intersection between the disciplines of cardiology and oncology (Lenneman et al. 2016). While the teamwork between cardiologists and oncologists already exists in certain medical centers, it is not yet an established specialty in all medical centers. The notion on characteristic cardiovascular late complications after cancer and the need for special surveillance led to the establishment of this new subspecialty to provide improved follow-up and to prevent, detect, and treat cardiovascular complications after early after cancer (Todaro et al. 2013).

The polymorphisms of genes associated with doxorubicin efflux transport and the metabolism of free radicals (NAD(P)H oxidase) are associated with the risk for anthracycline-associated cardiac heart failure (Wojnowski et al. 2005, Blanco et al. 2012, Armenian et al. 2013). Since chemotherapy including anthracyclines is necessary for the successful treatment of certain malignancies, the administration of anthracyclines may be compulsory, yet possibly risky for patients with known genetic variations for anthracycline-metabolizing genes. New drugs have recently been developed and have been introduced or are currently tested in pediatric cancer patients, such as the tyrosine-kinase inhibitor imatinib (pediatric chronic-phase CML), the Hedgehog signaling pathway targeting vismodegib (neuroblastoma and anaplastic large cell lymphoma), and the monoclonal cluster of differentiation (CD) 20-antibody rituximab (pediatric high-risk NHL) (Gore et al. 2013). Nevertheless, drug-related toxicity usually becomes apparent after sufficient follow-up, as shown by large and long-term trials, and the drug profile of all chemotherapeutic agents must be carefully analyzed. In the future, assessment of a personal genetic profile at the start of chemotherapy may be useful – or even necessary – for the planning of individualized, risk-based, and targeted cancer treatment. Information on any possible genetic susceptibility of anthracycline-related cardiotoxicity may identify cancer survivors at risk for cardiovascular late sequelae and influence the management of their cardiac long-term follow-up (Armenian et al. 2013). The goal of personalized medicine is to strategically plan individual cancer treatments with the aim of maximum survival and minimum toxicity (Figure 15).

Thus far, no consensus has been reached regarding cardiological interventions of childhood cancer survivors with cardiac complications (Armenian et al. 2015). In adult patients, betablockers and angiotensin-converting enzyme inhibitors have been used to treat left ventricular dysfunction and the same drugs have been recommended for treating cardiac complications in cancer survivors as well (Hunt et al. 2009). Only few

studies on the drug therapy of cardiac complications in childhood cancer survivors have been published (Lipshultz et al. 2002, Silber et al. 2004, Shaddy et al. 2007, El-Shitany et al. 2012). While enalapril, an angiotensin-converting enzyme inhibitor, was associated with a temporary improvement of the left ventricular function, there was no long-term benefit after 4 years (Lipshultz et al. 2002). In another study on pediatric cancer survivors, the use of the same drug resulted in an improvement (9%) of left ventricular end-systolic wall stress after one year. However, long-term effects remained unclear, since the median follow-up time was only three years (Silber et al. 2004). A prospective study on the effect of carvedilol, a betablocker, on symptomatic heart failure in pediatric patients did not show any beneficial effects (Shaddy et al. 2007). A larger study population and a longer follow-up may be necessary before firm conclusions on the value of medical interventions can be drawn. In newly diagnosed childhood ALL patients, carvedilol was administered during chemotherapy and seemed to have a protective role with respect to echocardiographic and biomarker values (El-Shitany et al. 2012). Further research on medical interventions intended to prevent and treat cardiovascular complications in this patient population is needed.

The four studies included in this thesis confirmed that cardiovascular morbidity and mortality after childhood cancer are higher than among controls. We provided unique long-term data on cardiovascular morbidity and mortality in both childhood and YA cancer survivors. Particularly long-term studies are very valuable for planning long-term cardiovascular surveillance programs.

This thesis has also provided new and valuable insights into the nature and occurrence of cardiovascular late adverse effects and mortality after YA cancer. The findings that the cardiovascular burden is increased after YA cancer provides essential information for setting up follow-up guidelines of YA cancer survivors, who are still at lack of specific surveillance. In the future, additional investigations with a special focus on young adult cancer are needed to fill this knowledge gap and to reduce the occurrence of late adverse effects in this growing cancer survivor population.

Many questions remain unanswered and it will be an immense challenge to balance maximally efficient cancer therapies with minimal long-term late sequelae. Pharmacological interventions are rare in childhood cancer survivors compared to adult cancer survivors, and larger studies with a longer follow-up of the impact of medical treatment ought to provide more information on the possibilities to reduce cardiovascular morbidity and, perhaps, to restore cardiac function. Ideally, personalized, risk-based cancer therapy will be available in the future to offer successful cancer therapy with a minimal risk for cardiovascular health complications (Figure 15). Nonetheless, cardiovascular surveillance after early onset cancer remains a lifelong cornerstone for the health care of cancer survivors, since the prevention and adequate treatment of cardiovascular late effects on time is essential. The aim is to offer survivors of cancer at an early age the best possible quality of life without fear of premature cardiovascular morbidity and mortality.

Before the cancer diagnosis at an adult age
- Preventive measures
- Improved screening
- Increased awareness

Personalized risk-based cancer therapy
- Screen for drug metabolizing polymorphisms (if available)
- Consider endogenous cardiovascular risk factors

Long-term follow-up
- Create an individual cardiovascular risk profile
- Plan scheduled medical tests based on this risk profile
- Modifiable risk factors!
- Medical (drug) intervention

Cancer diagnosis

Cancer treatment

Cancer treatment

Cancer survival

Quick diagnosis
- Molecular characterization
- Select the least cardiotoxic therapy, while retaining the same survival rates

Screening for cardiotoxicities during the treatment
- ECG and biomarkers based on protocol recommendations
- Documentation of cardiotoxic therapy in the survivorship passport

Figure 15: Overview of an optimal plan of the diagnosis of cancer, cancer therapy, and surveillance after cancer to reduce and perhaps prevent cardiovascular late adverse effects.

7 SUMMARY AND CONCLUSIONS

This thesis evaluated the cardiovascular burden after a cancer diagnosis below the age of 35 years. The key findings were:

* Both childhood and young adult cancer survivors were more likely to experience cardiovascular morbidity than the sibling cohort. The hazard ratios were highest after childhood cancer.
    o Among early onset cancer survivors, the risk for cardiomyopathy/ cardiac insufficiency was highest compared to siblings.
* Cardiac drugs and medications associated with the metabolic syndrome were more likely to be purchased by early onset cancer patients than by their siblings.
* The overall and cardiac-disease related standardized mortality rates were elevated among early onset cancer survivors. The mortality rates were highest after childhood cancer compared to the general population.

    o Cardiovascular health conditions were the leading non-malignant cause of death for early onset cancer survivors. The cumulative mortality due to cardiovascular conditions increased steadily over time until the end of follow-up.

* The risk for cardiovascular morbidity and mortality was strongly associated with the age at cancer diagnosis and the primary cancer diagnosis. The highest figures for cardiovascular morbidity and mortality figures were found after childhood cancer compared to siblings and to the general population.
* Among the cancer diagnosis groups, the cardiovascular health burden was highest after early onset acute leukemia (ALL, AML), lymphoma (HL, NHL), central nervous system tumor, malignant bone tumor, and testicular cancer. The burden was lowest for after early onset melanoma and thyroid cancer.

Taken together, the nationwide register-based studies I-IV of this thesis demonstrate that there is a markedly increased cardiovascular burden after cancer at a young age compared to siblings and the general population. This thesis provided novel data raising the concern for the well-being of patients who have received cancer treatment at an early age, since they have a high risk of developing cardiovascular complications later in life. Further data are required to analyze the long-term late cardiovascular adverse complications of early onset cancer therapies, particularly after young adult cancer. Owing to the excess cardiovascular burden of early onset cancer survivors described in this thesis, an individualized, risk-based, long-term cardiovascular surveillance is compulsory to ensure these survivors the best possible quality of life without the threat of severe cardiovascular sequelae.

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