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Coronary artery disease in survivors of childhood and early adulthood cancer

Syventävien opintojen kirjallinen työ

Syyslukukausi 2023

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Coronary artery disease in survivors of childhood and early adulthood cancer

Kliininen laitos

Syyslukukausi 2023

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Lääketieteellinen tiedekunta

TURUNEN, ROOSA: Coronary artery disease in survivors of childhood and early adulthood cancer

Syventävien opintojen kirjallinen työ, 29 s.
Lastentautioppi
Joulukuu 2023

Syöpähoitojen, erityisesti sädehoidon, tiedetään altistavan monien myöhäishaittavaikutusten lisäksi sepelvaltimotaudille, mutta vain muutamia tutkimuksia syöpähoitojen ja sepelvaltimotaudin välisestä laadullisesta yhteydestä on tähän mennessä tehty. Tämän tutkimuksen tavoitteena oli selvittää tarkemmin varhaisessa iässä sairastetun syövän ja sen hoitojen vaikutusta myöhemmin ilmenevän sepelvaltimotaudin luonteeseen sekä tarjota aiheesta uusia tutkimuskohteita tulevaisuutta varten. Lisäksi tavoitteena oli tulosten pohjalta arvioida elintapaohjauksen ja seurannan kehittämisen tarvetta sepelvaltimotaudin kehittymisen ehkäisemiseksi ja etenemisen hidastamiseksi. Oman tutkimuksen lisäksi opinnäytetyö sisältää kirjallisuuskatsauksen aiheesta.

Tutkimusjoukko muodostuu yhteensä 68 potilaasta, joilla on diagnosoitu syöpä ennen 35 vuoden ikää ja sepelvaltimotauti tämän jälkeen. Potilaat löydettiin Varsinais-Suomen sairaanhoitopiirin potilasrekisteristä diagnoosikoodien perusteella. Hoitokertomuksista etsittiin tarkemmin tietoa potilaiden henkilökohtaisista ominaisuuksista (ikä, biologinen sukupuoli, mahdollinen kuolinpäivä), syöpädiagnoosista ja -hoidoista, sepelvaltimotautidiagnoosista ja -hoidosta sekä perinteisistä sydän- ja verisuonitautien riskitekijöistä.

Lapsuudessa (0–17-vuotiaana) syöpään sairastuneilla sepelvaltimotauti diagnosoitiin 47,5 vuoden mediaani-iässä, mikä oli nuorena aikuisena (18–34-vuotiaana) syöpään sairastuneihin verrattuna 7,7 vuotta aikaisemmin. Rintakehän tai kokovartalon sädehoitoa saaneilla potilailla sepelvaltimotauti todettiin 8,6 vuotta nuoremmalla iällä kuin niillä, jotka eivät sädehoitoa rintakehän alueelle saaneet. Yhteensä 52 (76,5 %) potilasta hoidettiin invasiivisesti pallolaajennuksella tai ohitusleikkauksella, ja lähes kolmannes (N 17; 32,7 %) tarvitsi uusintatoimenpiteen myöhemmin. Tutkimuksen tulokset tukevat aiempaa tutkimustietoa syöpähoitojen sydäntoksisuudesta. Sen lisäksi tämä tutkimus osoitti syövästä selviytyneillä esiintyvän runsaasti sydän- ja verisuonitautien riskitekijöitä, sepelvaltimotauti todettiin potilailla nuoremmassa iässä normaaliväestöön verrattuna ja taudin luonne vaikutti vaikeahoitoisemmalta.

Avainsanat: syöpä, lapsi, nuori aikuinen, syövästä selviytyneet, myöhäisvaikutukset, sepelvaltimotauti

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1 INTRODUCTION

In Finland, around 150 children (<16 years old) and altogether nearly 900 children and young adults (<35 years old) are diagnosed with cancer every year (Finnish Cancer Register). Although there are currently around 7000 Finnish survivors of cancer diagnosed under the age of 25 (Finnish Cancer Register), only a small part of the survivors has reached the age of 50. Due to the development of diagnostic methods and anticancer therapies, the chances of survival have increased significantly since the 1970´s, 5-year survival rates reaching up to 80% (1–5). Whilst the number of long-term survivors is increasing and the survivors' mean age growing, the burden of therapy-related late effects also becomes more relevant in this population (4) Two thirds of childhood cancer survivors suffer from at least one chronic health condition, half of which are severe or life-threatening (4,5). The risk of morbidity and premature death has been proved to be higher among early-onset cancer survivors compared both with healthy siblings and the general population (4–8).

Remarkably, the risk for long-term effects increases even decades after the cancer diagnosis, and by 30 years, mortality rates for non-malignant late-effects or secondary malignancies exceed that from primary malignancy and its relapse (1,4,9,10). Among the survivors of childhood cancer, recurrence of the primary malignancy is known to be the leading cause of mortality, followed by second malignancies as well as cardiovascular and respiratory diseases as the highest non-malignant causes (4–8). A few available studies have proved cardiovascular diseases (CVD) to be the leading non-malignant cause for premature death among young adult cancer survivors as well (4,6,7). Therapy-related cardiotoxicity may appear as cardiomyopathy, heart failure, coronary artery disease (CAD), myocardial infarction (MI), valvular heart disease or arrhythmias (4–7,11). Mediastinal irradiation and chemotherapy with anthracyclines are known to predispose heart to the development of these complications (4–7,11). In addition to the therapy-induced exposure, the combination of the patient's cancer diagnosis, age at the time of diagnosis, gender, lifestyle, and genetic factors together form the risk of cardiac outcomes (4–7,11).

Although an association between anticancer therapies and later-onset CAD has been proven to exist, research data considering CAD is most found in studies with multiple other cardiac outcomes and only studied quantitatively, and a little is known about the nature of the developing ischemic condition (1,4–6). Even patients suffering from severe CAD can remain asymptomatic for years, and findings regarding subclinical changes after cancer treatment are of increasing interest (1). In this review, existing research data on cardiovascular morbidity among the survivors of early-onset cancer is gathered, focus on CAD and MI. A small sample size study of our own is also provided to gain a better understanding of the characteristics of the therapy-related CAD. The aim of this study is to evaluate the demand for further investigation on the nature of CAD among survivors of early onset cancer and evaluate whether the outbreak or at least progression of CAD among cancer survivors could be prevented with the right kind of follow-up and lifestyle guidance.

2 REVIEW OF THE LITERATURE

2.1 Morbidity and mortality from coronary artery disease after cancer at young age

As CAD is one of the leading causes of death among the general population, it's also one of the most common complications among survivors of childhood and young adulthood cancer (5). Due to cancer and the exposure to its treatments, studies have demonstrated the relative risk for CAD being up to 10-fold when compared with healthy siblings (5). A Scandinavian cohort study including 32,308 one-year survivors of childhood cancer (aged <20 years at cancer diagnosis) reported 8.1% of the survivors having been admitted to hospital at least once during the follow-up due to a CVD, of which 13.8% were for ischemic heart disease as the first cardiac hospital admission. Compared with population of 211,489 subjects, the overall relative risk for ischemic heart disease was 1.7 (95% CI: 1.5–1.9). Furthermore, the median age at the first

hospital admission due to a CVD was 35 years for the cancer survivors, which was reported to be on average seven years younger compared with the general population.(12)

A Finnish study based on the data of 13,860 5-year survivors of early-onset cancer (diagnosis at <34 years old) also reported a significant elevation on the risk for MI and cardiac ischemia compared to their siblings, with the overall HR of 1.8 (95% CI: 1.5–2.2) (4). According to another Finnish population-based register study, the cause-specific standardized mortality ratio (SMR) for cardiac ischemia and MI was increased at 1.9 (95 CI: 1.6-2.3) for all childhood and early adulthood cancer survivors, while the SMR for siblings stood at 0.8 (95% CI: 0.7-0.9). Interestingly, the SMR for the younger age group (0-19 years at diagnosis) was significantly higher (SMR 5.3 95% CI: 2.9-7.7) than the SMR of the older age group (20-34 at diagnosis, SMR 1.8 95% CI: 1.5-2.1).(6)

Survivors of certain types of cancer have turned out to be more predisposed to any cardiovascular complications than the others, with primary diagnoses of Hodgkin's lymphoma (HL), non-Hodgkin's lymphoma (NHL), testicular malignancies, leukaemia, and CNS tumours at the top (4–7,10,12). A large British cohort study of around 7000 survivors of HL reported over two-fold risk to die of MI (SMR 2.5 95% CI: 2.1-2.9) when comparing HL survivors with the general population (13). Mulrooney et al. found highest rates for MI in HL (HR 12.2 95% CI: 5.2-28.2) and neuroblastoma (HR 11.1 95% CI: 3.3-36.9) survivors. Of the studied cancer diagnostic groups, the lowest relative hazard was found in survivors of leukaemia (HR 3.3 95% CI: 1.2-8.6).(14)

Prasad et al. reported highest SMRs for death due to ischemia with survivors of HL (SMR 10.2 95% CI: 7.2-14.2) and NHL (SMR 4.0 95% CI: 1.5-8.6), while the risk for patients treated with CNS tumours was not elevated (SMR 0.6 95% CI: 0.01-3.1). This study too was able to present the correlation between CAD mortality and the age at the time of cancer diagnosis, with both HL and NHL survivors, the highest SMR in the adolescent age group (15-19 years at cancer diagnosis, SMR 16.3 95% CI: 5.3-38.1 for HL survivors and 19.5 95% CI: 2.4-70.4 for NHL survivors) and the lowest SMR in the young adult age group (20-34 years at diagnosis, SMRs 9.5 95% CI: 6.4-13.6 for HL and 2.3 95% CI: 0.5-6.6 for NHL).(7)

2.2 Cancer treatments

In addition to pathological effects due to the primary malignancy, higher cardiovascular morbidity of especially certain cancer types can be explained based on the anticancer therapies involved in their treatment. For example, HL is commonly treated with the combination of mediastinal irradiation and anthracycline chemotherapy, both considered highly cardiotoxic (1,4–7,12,14). Anthracyclines and radiotherapy both increase the risk of cardiovascular complications in relation to the dose. However, asymptomatic, latent cardiac damage has been observed as a consequence of even small doses, challenging the determination of cardiac safe dosages.(11,15) Other treatment related factors such as age at the time of treatment, administration route, combination of drugs, combination of chemotherapy and irradiation as well as size and anatomic location of the irradiation field also contribute to the risk of cardiotoxic outcomes (16).

Although separating radiation-induced late effects from those caused by anthracycline treatment isn't simple due to the tendency of combining the two treatment methods, clear evidence of CVDs after thoracic irradiation exists and clinical studies have demonstrated direct damage in coronary arteries and microvasculature, pericardial, myocardial, and vascular fibrosis as well as valvular stenosis (1,17,18). In coronary arteries, the irradiation results in acceleration of the atherosclerotic process and, eventually, CAD (17,18). Similarly, to CADs in the general population, the disease most often appears in the left anterior descending and the right coronary arteries with patients exposed to irradiation (1). Left main coronary arteries, however, are more likely affected after irradiation therapy than in the general population with CAD (1). By comparing the coronary computed tomography angiography (CTA) findings of asymptomatic, irradiation-treated HL and NHL survivors with those of healthy non-irradiated controls, CAD lesions were found to be more common, more proximally located, and severe and in larger areas in the cancer survivor group (19).

Mulrooney et al. suggested that even low irradiation doses of 15-35Gy can promote the dysfunction of coronaries (HR for MI 2.4 95% CI: 1.2-4.9 p=0.011), while doses exceeding 35Gy cause a significantly high risk for MI (HR 3.6 95 CI: 1.9-6.9, p<0.001)

(14). However, according to Tukenova et al. the risk of dying of a cardiovascular complication was significantly increased already with average doses of 5Gy and over (RRs 12.5 for 5-14.9Gy and 25.1 for >15Gy) (20).

The cardiotoxic nature of anthracyclines such as doxorubicin, daunorubicin, epirubicin and idarubicin, has also been studied. These studies have shown exposure to cumulative antracycline doses over 360mg/m^2 creating a four-fold risk (RR 4.4 95% CI: 1.3-15.3) for CVDs in general (20). The risk of congestive heart failure increases to two-fold with doses under 250mg/m^2 (HR 2.4 95% CI: 1.5-3.9) and to five-fold with doses over 250mg/m^2 (HR 5.2 95% CI: 3.6-7.4) when compared with patients who did not receive chemotherapy with anthracyclines (14,20). However, research data about anthracyclines as a risk factor for ischemic heart diseases specifically is limited and, for example, Mulrooney et al. found no significant association between anthracycline dose and an increased risk for MI (14).

Other non-anthracycline agents such as bleomycin, cyclophosphamide, cytarabine, cisplatin, some vinca alkaloids, and alkylating agents like ifosfamide have also been found cardiotoxic, yet little research data on their harmful cardiac effects exist and even less concerning those among children and young adults (1,4).

In the Nordic Childhood Cancer cohort study based on 37 515 cases collected from registries in the five Nordic countries, Garwicz et al. studied the trends between treatment eras (1960-1969, 1970-1979, 1980-1989 and 1990-1999) and mortality to further describe the association between the two. The results showed a significant decrease in non-cancer mortality (not specified) of 5-year survivors with HR of 0.64 in 1980-1989 (95% CI: 0.50-0.82, p<0.001) and 0.42 in 1990-1999 (95% CI: 0.30-0.60, p<0.001) with mortality rates of diagnostic era 1960-1969 as the comparison (HR 1). However, the overall standardized mortality ratio remains elevated even over 30 years after the initial cancer diagnosis, so the excess mortality among survivors of early onset cancer is not limited to the first years after cancer treatment. At 30 years of follow-up, the overall cumulative mortality was highest among survivors of HL, CNS tumour and leukaemia. Among HL survivors, the cumulative mortality was 27 %, and the most common causes of late death were result of non-cancer causes (10.0 %) and second cancer (7.4%). Among survivors with CNS tumours, the overall mortality at 30

years after the initial cancer diagnosis was 19 %, and the mortality was still mainly due to the primary cancer (11.7 %). Although causes of non-cancer deaths weren't specified further, ischemic heart disease was described as one of the dominating causes of death along cardiomyopathy in patients with HL in the 1970´s and 1980´s. In this study, no specified data on given treatments was available in the registries, which limits the outcome of the results.(10)

Kero et al. (2015) provided more specified data with cardiac ischemia or MI as cause of death among cancer survivors (aged 0-34 years at diagnosis) in three periods of time. The cumulative mortality for non-cancer causes was highest for CVDs, and the SMR for cardiovascular causes was highest among survivors of CNS tumour, HL and NHL. Some decrease in the hazard ratios for death due to cardiac ischemia and myocardial infarction was found between the treatment eras 1966-1979 (HR 2.6 95% CI: 2.0-3.8) and 1990-1999 (HR 2.1 95% CI: 1.0-4.4). During the latest treatment period, the HR was not significant compared to the sibling cohort (HR 2.1 95% CI: 1.0-4.4), but it is noteworthy that at the time of this study, this last population was still relatively young, and the cumulative mortality for cardiovascular causes begins to rise 15-25 years after the cancer treatment.(6)

In the previously mentioned Scandinavian cohort study by Gudmundsdottir et al. the patient cohort was also divided into four sub cohorts according to diagnostic periods of time. The risk for any CVD by the age of 40 increased from 9.6% with patients diagnosed in 1943-1959, described as prechemotherapy era, and 12.9% with patients in 1960-1974, described as first-generation chemotherapy era, to 16.2% in 1975-1989, early combination chemotherapy era, and 18.3% in 1990-2008, the late combination chemotherapy era. These results provided an opposite trend compared with the two previously mentioned studies, possibly providing evidence of the role of chemotherapy as an independent risk factor for cardiovascular complications. Again, no specific interpretation of CAD mortality was provided.(12)

2.3 Pathophysiology of the direct cardiotoxic mechanisms

With an additional stress that comes with the anticancer treatments, cancer itself is a known independent risk factor for the development of CAD. Endothelial damage, as a consequence of primary cancer and its treatment with both irradiation and chemotherapy, seems to be the main mechanism that further predisposes the arteries for the development of CAD. Cancerous cells can cause damage to endothelium by secreting numerous chemokines and cytokines that activate inflammation and promote atherosclerotic plaque formation. In addition, coagulation system is activated and coagulation factors such as thromboplastin and platelet activators are secreted.(16)

Different hypotheses for the mechanisms of anticancer therapy related cardiotoxic effects have been studied and presented, but the results are disputable and yet not entirely understood (21). Although many of the mechanisms are a natural part of aging, the processes are accelerated in tissues that are targeted with irradiation and anticancer agents (18). One of these mechanisms is the enhanced formation of reactive oxygen species (ROS) causing a condition called oxidative stress (18,21). Radiation therapy and anthracyclines are both known to produce ROS with multiple mechanisms that include activation of both mitochondrial and mitochondria-independent metabolic enzymes, and for example doxorubicin has been shown to stimulate the production by its strong ability to accumulate into mitochondria (1,18,21). Due to excessive amount of the free radicals, the antioxidant defense system is insufficient to prevent cells from all harmful effects, such as protein oxidation, lipid peroxidation and DNA damage, all of which can also lead to the activation of the cells' apoptotic pathways (21). By increasing the production of ROS, anticancer therapies have also been found to activate inflammatory pathways, and, in that way, to provide favorable surroundings for atherosclerotic plaque formation (1,17). Acute inflammation in the endothelial cells leads to formation of neutrophilic infiltration and slightly progressive fibrosis (1). The accumulating fibrin and platelets form thrombi, eventually resulting in obstruction of the lumen (1).

Another possible mechanism for radiation related cardiotoxicity is a less studied senescence of cells. Proliferating cells are more sensitive for irradiation than non-proliferating cells such as cardiomyocytes. Endothelial cells on the other hand, are metabolically more active than the cardiomyocytes, and it has been suggested that irradiation may induce a senescent phenotype in endothelial cells. This may be considered as a useful feature of irradiation therapy as it may inhibit the angiogenesis of the tumour. Senescent cells themselves don't proliferate but as their quantity grows due to irradiation, however, the immune system's ability to remove the senescent cells becomes insufficient, leading to accumulation in healthy tissues and causing pathologic conditions like CVDs. Although the metabolic activity of senescent endothelial cells remains, their function and gene expression are modified.(18)

In addition to overproduction of ROS, the senescent cells have been demonstrated to have a decreased expression of nitric oxide and thrombomodulin and an increased expression of cytokines, chemokines, adhesion molecules and plasminogen activator inhibitor 1 (PAI-1), all of which accelerate inflammation and formation of thrombosis and atherosclerosis in endothelial cells affected by irradiation (18,22). The increased levels of chemokines and adhesion molecules has been described as the onset of atherosclerosis, causing the monocytes to attach and form into foam cells (17,18). Some studies have also been able to demonstrate an increased permeability of senescent endothelial cells, an event which further leads to formation of plaques by encouraging the lipids to build up in the artery walls (1,18).

As endothelial damage in coronary arteries can lead to atherosclerotic process, whether the presence of high-fat diet and hypercholesterolemia is necessary for the development of CAD after cancer treatment, remains controversial. In some animal studies of CAD resulting from radiation therapy, a high-fat diet was observed as a requirement for the plaque development, while another study demonstrated similar changes even with a normal diet. At all events, all the studies had in common that the presence of high fat blood levels accelerate the process of plaque formation, indicating the role of a healthy diet in preventive care.(1)

2.4 Traditional CAD risk factors

Studies have shown that the development of atherosclerosis possibly begins already in childhood and early adulthood if traditional CAD risk factors like obesity, dyslipidemia, high blood pressure and glucose impairment are present (1,23). These factors are all criteria for a condition called metabolic syndrome, which together with inactive lifestyle, smoking and excessive drinking increases the risk for developing a heart condition (1). The Special Turku Coronary Risk Factor Intervention Project for children (STRIP) found that a low-saturated-fat diet intervention started as an infant was related to better endothelial function in boys as early as at the age of eleven, compared to the controls with no dietary intervention (23). In the Young Finns Study, the LDL-cholesterol and blood pressure levels, BMI and smoking in childhood were all significantly associated with adulthood intima-media thickness, measured as a sign of preclinical atherosclerosis (24).

With almost 30% of all children and adolescents being overweight in the United States, obesity is even more common among the childhood cancer survivors (1). As a healthy lifestyle would be considered as the best way to prevent CAD in the general population, studies have shown that the risk for metabolic syndrome or some of its components is increased in the survivors of childhood and early adulthood cancer survivors, not only because of poor activity and dietary habits or disabilities formed before, during or after the cancer treatment, but also from direct pathophysiological changes caused by the anticancer therapy (1,25).

A Finnish population-based study was able to demonstrate a higher likelihood of purchasing medications for hypertension and diabetes in both childhood and young adult cancer survivors when compared with siblings, and an increased likelihood of purchasing lipid-lowering medication in young adult survivors (26). This reflects the increased existence of CVD risk factors and therefore an increased CAD morbidity among cancer survivors.

2.5 Treatment-related development of metabolic syndrome

One of the suggested pathophysiological mechanisms for developing a metabolic disorder include obesity-related alterations in adipocyte hormone secretion, possibly referring to central leptin resistance (25,27). Alterations in leptin receptors and leptin sensitivity affect energy metabolism and induce hunger (1). A study including 116 acute lymphoblastic leukaemia (ALL) survivors was able to demonstrate increased levels of leptin and decreased levels of adiponectin, both associated with insulin resistance (25,27). Levels of leptin were also related to higher measures of body fat and were reportedly higher in female and those treated with cranial radiotherapy, while insulin resistance occurred independent of gender, body mass index and treatment methods (25,27). Cranial radiotherapy is also shown to predispose to decreased secretion of growth hormone and, as growth hormone is known to regulate adipocyte metabolism and insulin sensitivity, this further leads to weight gain and the development of type 2 diabetes (1).

Both preclinical and clinical studies have been able to show that radiation-induced pancreatic changes such as islet cell necrosis and mitochondrial destruction also play a role in the development of type 2 diabetes mellitus (25). In a review article by Barnea et al, the American Childhood Cancer Survivor Study (CCSS) comparing pediatric cancer survivors to their siblings, found total body irradiation (TBI) to form an independent risk for both diabetes and dyslipidemia, while another reviewed study found similar results simultaneously observing that blood pressure or waist circumference weren't significantly changed. However, a reviewed study including childhood stem cell transplant survivors also treated with TBI found the patients to have a two-fold risk for hypertension when comparing with patients not treated with TBI. The presence of some metabolic syndrome criteria such as hyperglycemia even on a normal weight cancer survivor could be explained by the hypothesis of TBI altering the body composition as amount of muscle mass is decreased and visceral fat increased due to the cancer treatment.(25)

Some study data has also suggested that alterations in intestinal microbiota resulting from chemotherapy or dietary factors can cause insulin resistance and obesity (25).

High doses of steroids included in some stages of anticancer treatment have also been found to grow appetite and lower lean body mass (1).

2.6 Dietary habits

Some more specified research data on dietary habits and diet quality during and after cancer treatments among childhood and young adult survivors exist. What most of these studies' results have in common, is that adherence to nutritional guidelines among adult survivors is commonly poor (25,28). This manifests as higher intake of carbohydrate-based meals and excessive consumption of saturated fats, salt, and sugar, while consumption of fiber- and calcium-containing foods, vegetables and fruit is inadequate (25,28). These unhealthy alterations in dietary habits most likely originate from health professionals' and parents' strategies to compensate the decreased oral intake of the patient (28). Cancer treatments can cause symptoms like nausea, vomiting and changes in taste, all leading to decreased appetite and motivation to eat (28). A study consisting of twenty-two childhood ALL and Lymphoma survivors reported that the patients´ food cravings were most likely directed towards fast-foods, while the cravings had no significant effect on weight during 12 month-follow up (29). As important it is for the patient to avoid significant weight loss and malnutrition, encouraging to unhealthy, high-energy diet during the treatments can become a permanent habit later in life (28).

2.7 Physical activity

Compared with healthy population, most studies have proved childhood cancer survivors to be significantly more prone to physical inactivity during adulthood (25). As physical activity is known to be beneficial for cardiac health, a study with survivors of

HL showed up to 51% decrease in the risk for cardiovascular incidents among survivors whose activity levels reportedly met national vigorous activity guidelines (30).

Some studies on the effects of physical activity increasing interventions among childhood and young adulthood cancer survivors have been performed, both during and after cancer treatments. For example, Braam et al gathered six studies concerning physical activity increasing intervention within 5 years since the diagnosis in a Cochrane systematic review. Altogether 171 survivors of childhood ALL were included. Although the quality of the results was decreased by small sample sizes and other methodological limitations, the studies were able to demonstrate some positive effects such as cardiorespiratory fitness, body composition and health-related quality of life.(31)

An intervention study from Finland was able to show beneficial effects on cardiometabolic risk factors after a 16-week home-based exercise program performed by seventeen ALL childhood survivors aged 16 to 30 years. As other studies have proved ALL patients to have been inclined to an inactive, sedentary lifestyle and poor physical fitness, this study showed significant improvements in fasting insulin, presence of insulin resistance and fat percent after a simple, low-cost exercise intervention, and the number of patients with metabolic syndrome was halved. Similarly to previous studies, this study wasn't able show significant changes in body weight or BMI, possibly due to growth of muscle mass and lack of changes in diet. However, the results indicate to the correlation between physical activity, lower visceral fat, and decreased CVD risk, regardless of BMI.(32)

3 METHODS

3.1 Review data

PubMed was searched to find articles considering cancer therapy related cardiac outcomes and late effects in general in childhood, adolescent, and young adult (AYA) cancer survivors. The search results were limited by English language, publication date to articles published after the 2000s, and full free accessibility. The eligibility of the articles was evaluated based on the titles and the content of the abstracts. The final version of this review is based on 28 English-written articles (References 1, 4-7, 10-32) found on PubMed.

3.2 Study subjects

Permission for research was applied for from the hospital district of Southwest Finland (permission number T08/008/20). The cases included in the study were identified from the hospital district's patient register with the following criteria: a diagnosis with cancer before the age of 35 (0-34,99 years) and a diagnosis of coronary artery disease made after the cancer diagnosis at any age. Cancer diagnoses were identified with diagnosis codes 140-209 from ICD-8 and ICD-9, and C00-C97 from ICD-10. Diagnosis codes 410-414 from ICD-8 and ICD-9, and I20-I25 from ICD-10 were used to identify CAD diagnoses. Data was collected from the first date when patient diagnoses were electronically available (1/1/1977 or earlier if possible) until diagnoses made by 31/12/2019.

Altogether 106 cases were identified from the register. Patient data were then manually reviewed from health reports available in the electronic health care system, and in 61 cases the information was supplemented with patient data ordered from the

archives in paper form. Health reports were searched for personal data (date of birth, biological sex, is patient alive), details about both cancer (diagnosis, diagnosis age, possible recurrence or new malignancy, cancer treatments) and CAD (diagnosis, age at diagnosis, time between cancer and CAD diagnoses, possible symptoms, examinations and cardiac follow-up, line of treatment, CAD medications and other CVDs) and information about traditional CAD risk factors (family history, smoking, blood pressure, body mass index (BMI), physical activity, blood lipid levels).

Based on the manual review of all 106 health reports, 38 of the cases were excluded, 17 cases for faulty cancer diagnosis, 15 for faulty heart diagnosis and five for both. In one case the ischemic heart condition was diagnosed prior to the cancer diagnosis and was therefore excluded as well. Altogether 68 cases were suitable for the study as the criteria for both cancer and CAD diagnoses were met. The study subjects were divided into two subgroups based on age at cancer diagnosis. In this thesis, the group of 0–17-year-olds at the time of cancer diagnosis are referred to as the childhood cancer survivors and the 18–34-year-olds as the young adulthood survivors.

4 RESULTS

The final study population consisted of 68 cancer survivors (Figure 1), of whom 11 were diagnosed in childhood (0-17 years old) and the remaining 57 in early adulthood (18-34 years old). Forty-eight (70.6%) out of all 68 study subjects were male (Table 1). All patients were born between 1943-1974 and 46 (67.6%) survivors were still alive in February 2020 when the research started. Based on the time of first MI and the date of death, no sudden deaths due to MI occurred during the research period.

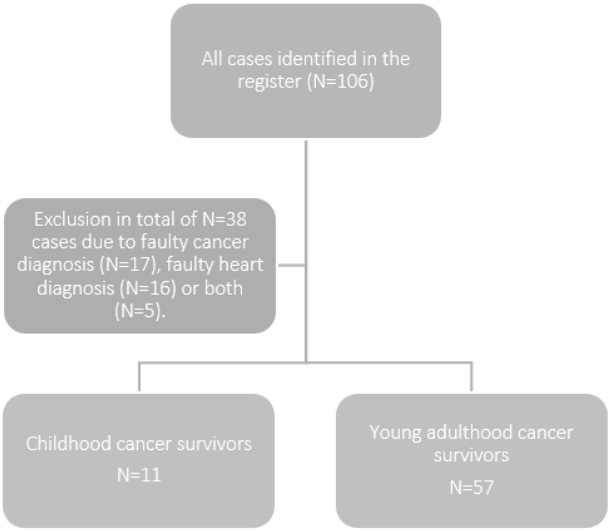

Figure 1. Overview of the formation of the final study population as described in the methods. Eligible cancer survivors were divided into childhood cancer survivors (age 0-17 at cancer diagosis) and young adulthood survivors (age 18-34 at diagnosis)

Table 1 shows the distribution of cancer diagnoses among all study subjects. Lymphomas were the most common types of cancer among both age groups and biological sexes. Among young adult survivors, the second most common cancer types were breast cancers in females and testicular cancers in males. Twenty (29.4%) patients were diagnosed with either recurrence of the primary cancer or development of a new malignancy before CAD was diagnosed.

Table 1. Characteristics of all study subjects by age groups. *Other cancer types (N): cervical cancer (2), osteosarcoma (2), thyroid cancer (2), brain tumour (1), liposarcoma (1), ocular melanoma (1), polycythaemia vera (1), thymus cancer (1), von Hippel-Lindau with multiple tumours (1).

	Age at cancer diagnosis		
	0-17 years (n=11)	18-34 years (n=57)	All study subjects (n=68)
Characteristics	**N (%)**	**N (%)**	**N (%)**
Biological sex			
Female	1 (9.1)	19 (33.3)	20 (29.4)
Male	10 (90.9)	38 (66.7)	48 (70.6)
Primary cancer diagnosis			
Hodgkin´s lymphoma	7 (63.6)	21 (36.8)	28 (41.2)
Non-Hodgkin's lymphoma	3 (27.3)	4 (7.0)	7 (10.3)
ALL	1 (9.1)	2 (3.5)	3 (4.4)
Testicular cancer	0 (0.0)	8 (14.0)	8 (11.8)
Breast cancer	0 (0.0)	6 (10.5)	6 (8.8)
Skin cancer	0 (0.0)	4 (7.0)	4 (5.9)
Other cancer types*	0 (0.0)	12 (21.1)	12 (17.6)
Alive on 1.2.2020	8 (72.7)	38 (66.7)	46 (67.6)
Total	11 (100)	57 (100)	68 (100)

Chemotherapy was administered for 42 (61.8%) patients, and nearly half of these patients (20 patients, 29.4 % of the cohort) had received treatment with anthracyclines. Forty-one (60.3%) patients were treated with chest irradiation or TBI. Altogether 13 (19.1%) patients were exposed to both anthracyclines and radiotherapy to the chest, and 19 (27.9%) patients were treated with neither. For 7 patients (10.3%), surgery was the only cancer treatment.

The distribution of primary cancer treatment time by decades is presented in Figure 2, and the median diagnostic ages for both primary cancer and CAD in Table 2. The median age at CAD diagnosis was 47.5 years (range: 31.6-59.0) in the childhood cancer survivors' group and 55.2 years (range: 24.8-72.5) in the AYA survivors' group. Among the 41 (60.3%) survivors whose cancer treatment had

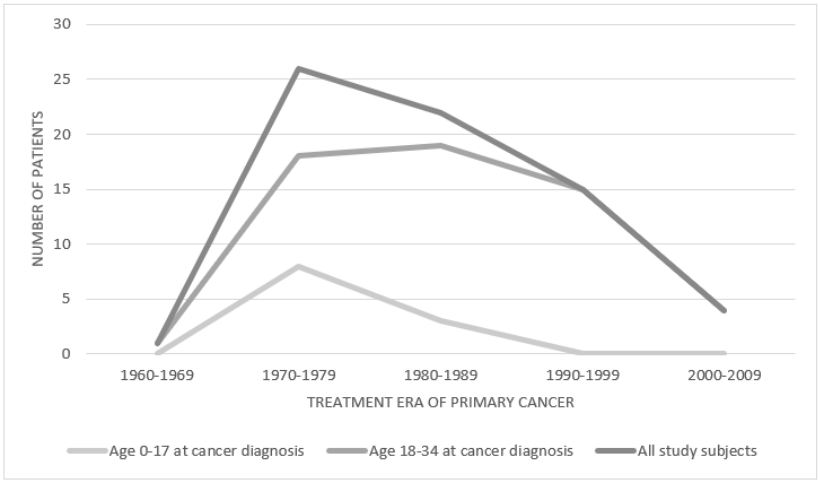

Figure 2. Number of patients in relation to time of treatment of primary cancer. If cancer treatments were administered over two different decades, the decade in which most of the treatments were focused on was selected for the results.

Table 2. Diagnostic ages at the time of cancer and chronic CAD or first MI, and the time between the two, by age groups and treatment exposure.

	Age at cancer diagnosis (Years)			Age at CAD diagnosis (Years)			Time between cancer and CAD diagnoses (Years)		
	Median	Range	IQR	Median	Range	IQR	Median	Range	IQR
All study subjects	27.3	7.3-34.8	23.1-32.3	53.4	24.8-72.5	45.4-58.7	24.4	0.3-42.4	19.1-34.0
Treatment exposure									
Chest radiation or TBI	24.7	0.0	20.3-31.8	48.6	0.0	43.7-55.7	23.4	0.0	16.0-34.0
No chest radiation or TBI	30.3	0.0	26.9-32.7	57.2	0.0	49.2-60.8	27.5	0.0	21.3-33.8
Childhood (0 to <18 years)	15.6	7.3-17.8	13.1-17.6	47.5	31.6-59.0	39.2-52.7	34.4	20.2-42.0	25.1-35.8
Treatment exposure									
Chest radiation or TBI	15.1	7.3-17.8	12.8-17.6	46.5	31.6-54.7	37.8-50.8	33.9	20.2-37.0	22.5-35.7
No chest radiation or TBI	17.0			59.0			42.0		
Young adulthood (18 to <35 years)	30.3	20.3-34.8	25.4-32.6	55.2	24.8-72.5	45.8-60.4	23.9	0.3-42.4	16.1-32.5
Treatment exposure									
Chest radiation or TBI	26.6	20.4-34.7	23.6-32.5	49.4	24.8-69.4	44.9-57.4	22.6	4.5-42.4	15.3-29.4
No chest radiation or TBI	30.3	22.6-34.8	27.2-32.9	57.1	33.7-72.5	48.1-60.8	26.7	0.3-38.2	21.3-33.3

included chest radiation or TBI, the median age at CAD diagnosis was 48.6 years (range: 24.8-69.4), which was on average 8.6 years earlier compared to the 27 (39.7%) survivors who hadn't been exposed to chest irradiation or TBI.

Out of all survivors who suffered from MI, the median age at the first MI was 48.8 (range: 31.6-59.0) in the childhood survivors´ group and 47.0 (range: 24.8-72.5) in the young adulthood group. Little difference between biological sexes was found, as the median age of the first MI was 46.9 years (range: 24.8-72.5) in males and 47.1 years (range: 34.5-59.0) in females.

4.1 Cardiovascular follow-up after cancer treatments

Only in 3 of the 68 studied cases (4.4%), a regular heart-specific follow-up was mentioned in the health reports, although in 17.6% of the cases a mention of the cardiotoxicity of the cancer treatments was found in health reports either during cancer treatments or in connection with CAD diagnosis. In 76.5% of the cases, regular medical check-ups including cardiac auscultation and chest x-rays were reported after cancer but no mention of a more comprehensive examination, for example heart ultrasound, was found during follow-up. In these cases, more detailed examinations were performed only after patient had reported CAD related symptoms.

4.2 CAD and other cardiovascular health

Over half (N 37: 54.4%) of the cancer survivors with CAD had suffered from MI during the research period, and in 30 (81.1%) of these cases, MI was the first ischemic heart diagnosis, based on the date of MI diagnosis and the lack of CAD diagnosis prior to that. In the group of young adulthood survivors, 30 (52.6%) out of the 57 survivors suffered from MI. The prevalence of MIs among the childhood cancer survivors´ group was relatively higher, as 7 (63.6%) out of all 11 survivors had MI. Seven (35.0%) of the female survivors and 30 (62.5%) of the male survivors had MI, and 81.1% of all infarction cases were male. Twenty-one (56.8%) of all MI patients had received chest irradiation or TBI during cancer treatments.

Fifty-two (76.5%) of the cancer survivors were treated invasively with percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), as for 15 (22.1%) patients, the line of treatment remained non-invasive by the time research period ended. CABG was the first invasive treatment method for 20 (29.4%) patients. Nearly third (N 17: 32.7%) of all invasively treated patients required a reoperation later.

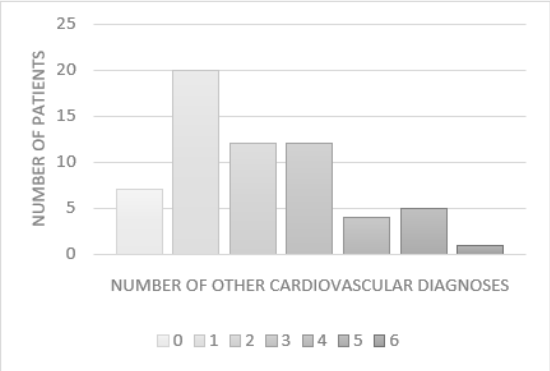

Figure 3. The number of other CVD diagnoses besides CAD. Other diagnoses include valvular, myocardial, and pericardial diseases, heart failure, hypertension, arrhythmias, conduction disorders, cerebrovascular disorders, peripheral arterial disease, and deep vein thrombosis.

Overall cardiovascular health was assessed by the number of other cardiovascular diagnoses besides CAD (Figure 3). The mean number of other cardiovascular diagnoses per person was 2.1 (range: 0-6) among all survivors. In 7 cases (10.3%) CAD was the only cardiovascular diagnosis as 32 (47.1%) of the survivors were diagnosed with 1-2 other CVDs. Eight out of the ten people diagnosed with 4 or more other cardiovascular conditions had received chest irradiation or TBI during cancer treatments.

As pictured in Figure 4 (a-b), the use of statins, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), acetylsalicylic acid (ASA), beta blockers and calcium channel blockers was evaluated, as it describes, in addition to the treatment of CAD, the treatment of its risk factors and thus the prevalence of risk factors. Information on medications was collected from the closest available time point to the CAD diagnosis, and therefore whether the medications were already in use before the diagnosis is not considered in the results. Beta blockers (N 54: 79.4%) and statins (N 50: 73.5%) were the most prescribed medications with ASA (N 44: 64.7%) as the third. For 19 patients (27.9%), 4 or all 5 of these medications were prescribed. Only in 6 (8.8%) patients, no mention of any of the four antihypertensive medication groups (ACE-inhibitors, ATBs, beta, and calcium channel blockers) was found.

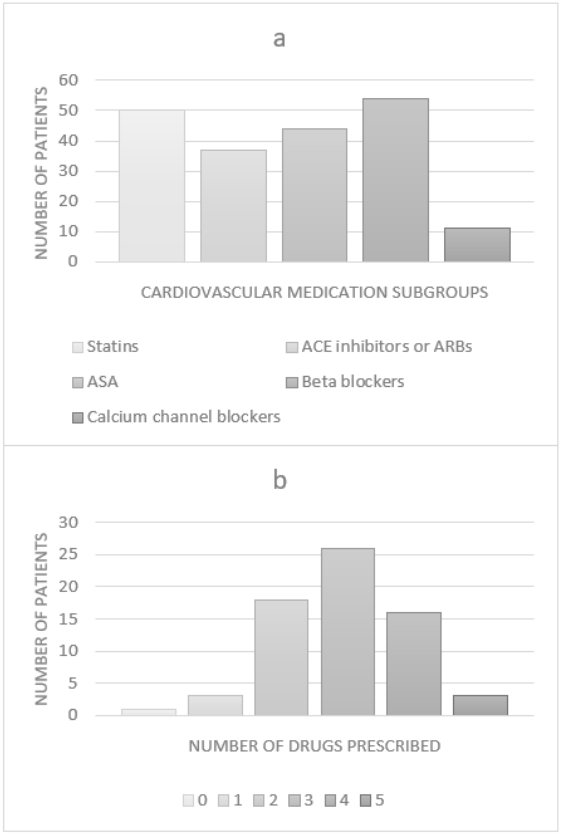

Figure 4. (a-b) The use of cardiovascular medication. (a) The number of patients to whom each drug was prescribed. (b) The number of patients in relation to the number of different cardiovascular drugs prescribed.

4.3 Risk factors

The prevalence of traditional CAD risk factors among patients was assessed by collecting data on biological sex, positive family history, blood pressure, blood lipid levels, smoking, and BMI. Systemically recorded information on physical activity could

Table 3. Prevalence of cardiovascular risk factors by age groups. * The measured values are from the closest available time point in relation to the CAD diagnosis date.

Risk factors	Age 0-17 at cancer diagnosis (n=11) N (%)	Age 18-34 years at cancer diagnosis (n=57) N (%)	All study subjects (n=68) N (%)
Biological sex			
Male	10 (90.9)	38 (66.7)	48 (70.6)
Female	1 (9.1)	19 (33.3)	20 (29.4)
Family history			
Positive family history for CAD	4 (36.4)	16 (28.1)	20 (29.4)
Negative family history for CAD	1 (9.1)	10 (17.5)	11 (16.1)
Information missing	*6 (54.5)*	*31 (54.4)*	*37 (54.4)*
Smoking			
Regular smokers	4 (36.4)	33 (57.9)	37 (54.4)
Non-smokers	5 (45.5)	23 (40.4)	28 (41.2)
Information missing	*2 (18.2)*	*1 (1.8)*	*3 (4.4)*
Body Mass Index (BMI) *			
BMI ≥ 30	2 (18.2)	16 (28.1)	18 (26.5)
BMI < 30	8 (72.7)	41 (71.9)	49 (72.1)
Information missing	*1 (9.1)*	*0 (0.0)*	*1 (1.5)*
Blood pressure*			
High blood pressure (≥ 140/90 mmHg)	3 (27.3)	23 (40.4)	26 (38.2)
Normal blood pressure (< 140/90 mmHg)	6 (54.5)	32 (56.1)	38 (55.9)
Information missing	*2 (18.2)*	*2 (3.5)*	*4 (5.9)*
Blood lipid levels*			
LDL cholesterol			
High LDL cholesterol (≥ 3.0 mmol/l)	4 (36.4)	26 (45.6)	30 (44.1)
Normal LDL cholesterol (< 3.0 mmol/l)	4 (36.4)	24 (42.1)	28 (41.2)
Information missing	*3 (27.3)*	*7 (12.3)*	*10 (14.7)*
HDL cholesterol			
Low HDL cholesterol (<1.0 mmol/l for men, < 1.2 mmol/l for women)	4 (36.4)	13 (22.8)	17 (25.0)
Normal HDL cholesterol (≥ 1.0 mmol/l for men, ≥ 1.2 mmol/l for women)	4 (36.4)	37 (64.9)	41 (60.3)
Information missing	*3 (27.3)*	*7 (12.3)*	*10 (14.7)*
Triglyceride			
High triglyceride (≥ 1.7 mmol/l)	5 (45.5)	11 (19.3)	16 (23.5)
Normal triglyceride (<1.7 mmol/l)	3 (27.3)	37 (64.9)	40 (58.8)
Information missing	*3 (27.3)*	*9 (15.8)*	*12 (17.6)*
Abnormality of at least one lipid measurement	7 (63.6)	34 (59.6)	41 (60.3)

not be found in health reports and therefore it wasn´t considered in the results. 31 (45.6%) of all cancer survivors had 3 to 4 risk factors

for CAD, and 10 (14.7%) patients had even more. Only 14 (20.6%) of the patients had 0 to 2 risk factors. In 13 (19.1%) patients more than one risk factor was unknown, and the total amount of risk factors could not be assessed. Family history was the most frequently missing information as for 37 (54.4%) of the patients, no mention of family history was found, or family history was otherwise unclear.

The prevalence of risk factors is presented in Table 3. Male gender (N 48: 70.6%), dyslipidaemia (N 41: 60.3%) and smoking (N 37: 54.4%) were the most common traditional risk factors among all survivors. At least one of the blood lipid level measurements was abnormal in 41 (60.3%) patients, with high LDL cholesterol level as the most frequent (N 26: 45.6%) abnormality among young adulthood survivors and high triglyceride (N=5: 45.4%) among childhood survivors. At the time of CAD diagnosis, only 18 (26.5%) patients were obese (BMI ≥30) and 26 (38.2%) had hypertension.

5 DISCUSSION

To summarize one of the main findings in this study, the results were consistent with previous knowledge on the cardiotoxic nature of cancer treatments by showing that CAD mainly occurred in patients who had received irradiation therapy as part of their cancer treatment. This is also supported by the fact that majority of the patients were diagnosed with the types of cancer that are typically treated with irradiation. In addition to CAD, this study demonstrated a variety of cardiovascular comorbidities among childhood and AYA cancer survivors. Of note is, that only one fourth (26.5 %) of the patients were overweight at the time of CAD diagnosis.

From the point of view of follow-up, prevention and early diagnosis, an interesting finding in this study was that for 44.1% of the patients, their first MI was also the first manifestation of CAD, and this number was even higher (71.4%) among the childhood survivors. However, existing research data shows that in the general population, ischemic heart diseases are diagnosed with MI as the primary diagnosis in up to 50% to 70% of the cases (33,34). This, together with the lack of any sudden deaths due to MI, suggests that in the present study the CADs were found at an early stage relatively often. A notable finding, however, was that in the present study, diagnosis ages were younger than those of general population. Among all cancer survivors, the first MI was diagnosed at median age of 47.0 years. For example, in the US, the average ages at first MI among general population are 72.0 in females and 65.6 in males (35). Younger

age at cancer diagnosis and treatment methods were both found to affect the age of CAD diagnosis, as CAD was diagnosed in average more than half a decade earlier in childhood survivors and those who had received chest irradiation or TBI.

Although the relative share of PCIs among the invasive treatment methods is increasing, the total amount of revascularization therapies has decreased due to advanced medical treatment and increased questioning of the need for invasive treatment in stable CAD (36). In 2016, only 31.4% of the invasive therapies were CABGs and 68.6% PCIs in the US general population. Most significant factors affecting the choice of treatment method are, that PCI is more commonly used to treat acute angina or threatening MI with limited number of damaged arteries, as more stable and multi vessel patients are treated with CABG (37). In the present study, 38.5% of the first invasive CAD treatments were CABGs, which is a slightly bigger proportion than in the US population. This can possibly be explained by a trend that has occurred over the years, rather than by more difficult manifestation of CAD among cancer survivors alone.

However, the number of reoperations among patients was seemingly high in the present study, as nearly third of the invasively treated patients required a reoperation later. In comparison, in a study by Loponen et al, among 662 CAD patients from general population, 17.3% of PCI patients and 3.2% of CABG patients were reoperated during a 3-year follow-up (37). Another study found that out of radiation-treated lymphoma patients, 85.7% developed coronary restenosis after coronary stenting, whereas the incidence of restenosis between non-radiated lymphoma patients (16.7%) and general population (25.5%) did not differ significantly (38). These results support the role of cancer treatments, especially irradiation therapy, in the development of coronary stenosis and restenosis among cancer survivors, indicating that CAD caused by cardiotoxic cancer treatments is of a different nature, and, therefore possibly more difficult to treat than CAD among the general population.

In a CCSS cohort including 8599 survivors of childhood cancer, having 3 to 4 risk factors of cardiovascular risk factor cluster (CVRFC) was reportedly associated with a higher risk for cardiac events. While three of the CVRFC risk factors, hypertension, impaired glucose tolerance and dyslipidemia were more common among the survivors, the

prevalence of the fourth factor, obesity, was found similar in the childhood cancer survivors (20.6%) and their siblings (20.8%). Even though the risk for most of the CVRFC factors was higher among survivors, the overall risk for CVRFC was not increased when compared to siblings.(39) Although the studied risk factors in the present research differed from those in the CCSS, over half of the cancer survivors exceeded the limit of three commonly known risk factors of CAD, even with the low prevalence of obesity (26,5%).

In addition to the low prevalence of obesity, the prevalence of hypertension (N=26: 38.2%) was surprisingly low in the present study. To compare the numbers with general population, one study based on national survey data from the 1990s found prevalence of hypertension among adults over 35 years of age to be 44% in European countries (40). In the US population, the prevalence is estimated at 34.0% in adults over 20, with prevalence of 11.6% among adults aged 20 to 39; 37.3% among ages 40 to 59 and 67.2% among adults over 60 years (35). Before this, multiple studies have found hypertension to be more common in childhood and AYA cancer survivors than general population, and according to the CCSS, long-term survivors with mean age of 32 have twice the risk of hypertension compared to their siblings (1,25,41,42). Some studies have also found the use of antihypertensive medication to be more common or similar among childhood and AYA cancer survivors compared with healthy controls (43). Almost all of the patients in the present study had been prescribed at least one antihypertensive drug, and because the results did not take into account whether the drugs were prescribed before or after the CAD diagnosis, it is possible that in reality a higher proportion had a history of high blood pressure, which would also be in more concordance with other studies.

A meta-analysis study evaluated risk behaviour of childhood cancer survivors based on smoking and use of other substances. As 22% of the survivors were reported to smoke regularly, their siblings and other peers were even more likely to smoke.(44) In the present study over half of the patients had reported regular smoking, which also exceeds the rates in the US, where regular cigarette smoking has decreased from 40% in 1964 to 13.7% in 2018 (36).

Since this study is based on those patients with both a cancer diagnosis and a subsequent CAD diagnosis treated within the same hospital district, the study does not take into account patients who were treated elsewhere for the other diagnosis. Therefore, the results are not sufficient to describe the incidence and morbidity of CAD after cancer treatments in general. In addition, the research group is moderately small due to the relatively poor prognosis of many cancers before the 1980's, and the fact that only a small part of the patients who got cancer as children have already reached the age of fifty, which is significant from a cardiovascular point of view. Another weakness is, that not all of the studied data was systemically recorded in health reports and therefore, data availability was variable between patients, and consistent time points for different variables could not be determined. However, the method of data collection in this study can be considered more of a strength, as the research is based on thorough review of medical records and the qualitative information obtained from them, while many previous studies rely on simpler information based on diagnosis or procedure codes.

All patients were diagnosed with cancer before the 2000s, when no consistent international follow-up recommendations for CAD after cancer have been available. According to the surveillance recommendations by The International Late Effects of Childhood Cancer Guideline Harmonization Group, IGHG, childhood and young adulthood cancer survivors whose heart has been exposed to irradiation during cancer treatment, should be informed of the increased risk for CAD. Based on current research data, recommendations for routine CAD surveillance couldn´t have been formulated. However, surveillance and management of modifiable cardiovascular risk factors in accordance with national guidelines is strongly recommended, timing and frequency of the surveillance based on individual characteristics and risk for CAD, but from the age of 40 at the latest and at a minimum of every 5 years.(45)

Since cancer treatments have developed over the past decades and the prognosis of cancer is improving, more and more childhood and AYA cancer survivors will live long enough to face the late effects, including CAD. The present study showed, in agreement with previous research data, that in childhood and AYA cancer survivors, cancer treatments, especially irradiation therapy, predispose to CAD later in life.

Moreover, most survivors had several cardiovascular risk factors, CAD was diagnosed at a younger age than in the general population, and the nature of the disease seemed more difficult to treat. Based on the results and the IGHG recommendations, more attention should be paid to the lifestyle guidance of children and young adult cancer survivors, as well as the monitoring of risk factors in a timely and proactive manner. Findings about the possibly more severe nature of the disease provide interesting research opportunities for treatment-induced CAD in the future.

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