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

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ABSTRACT

Purpose: Childhood cancer survivors are at risk for developing metabolic syndrome (MetS), which subsequently leads to cardiovascular morbidity and excess mortality. Our aim was to investigate the purchases of medications associated with MetS among 7551 early onset cancer patients compared to siblings.

Methods: Our nationwide Finnish population-based registry study analyzed the drug purchase of medication among early onset cancer patients diagnosed with cancer below the age of 35 years between 1994 and 2004 compared to siblings by linkage to the drug purchase registry, allowing for a maximal follow-up of 18 years.

Results: The hazard ratios (HRs) for purchasing antihypertensives and diabetes drugs were higher after both childhood (HR 4.6, 95%CI 3.1–7.0; HR 3.0, 95%1.5–6.1) and young adulthood (YA) cancer (HR 1.5, 95% CI 1.3–1.8; HR 1.6, 95%CI 1.1–2.2) compared to siblings. The HRs for purchasing lipid-lowering drugs were elevated both after childhood (HR 4.3,95%CI 0.9–19.5) and YA cancer (HR 1.6, 95%CI 1.04–2.5), but only reached significance in YA cancer patients. Among specific cancer diagnosis groups, highest HR values for antihypertensives were found in childhood acute lymphoblastic leukemia (ALL) (HR 6.1, 95%CI 3.7–10.3) and bone tumor (HR 4.3, 95%CI 1.9–9.4), and YA ALL (HR 4.8, 95%CI 3.1–7.0) and acute myeloid leukemia (AML) (HR 3.4, 95%CI 2.5–5.1) patients. Moreover, childhood ALL (HR 6.3, 95%CI 2.7–14.8), AML (HR 7.6, 95%CI 1.9–24.5) and central nervous system (CNS)-tumor (HR 3.5, 95%CI 1.3–9.2) and YA ALL (HR 3.7, 95% CI 1.2–9.5) patients showed the strongest likelihood of purchasing diabetes drugs compared to siblings.

Conclusion: The purchase of medications associated with MetS was increased after early onset cancer and highly dependent on the age at cancer diagnosis and the cancer diagnosis. Prevention strategies are imperative for reducing potentially life-threatening cardiovascular complications after early onset cancer.

1. Introduction

While solid survival rates after early onset cancer reflect the advances in treatment [1,2], there has been great concern regarding long-term morbidities due to cancer therapy [1–6]. Excess late mortality is attributable to the severe late effects threatening a growing population of early onset cancer survivors [7–11].

Morbidity after childhood cancer has been shown to be remarkably high [3,5]. Two in three childhood cancer survivors are likely to suffer from long-term complications [4]. At the age of 45 years, more than 90% of childhood cancer survivors have reported a chronic health problem with over 80% reporting a life-threatening disease [3]. Cardiovascular complications after cancer therapy represent the most common and severe non-malignant morbidities [12,13].

The metabolic syndrome has been defined as a cluster of clinical risk factors for cardiovascular disease, such as obesity,

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hypertension, hypertriglyceridemia, hyperglycemia, and insulin resistance, which can eventually lead to diabetes mellitus type 2 [14,15]. Childhood cancer survivors have been found to be more susceptible to develop characteristics of metabolic syndrome than the general population, which further amplifies their risk of cardiovascular late effects and excess mortality [16–18]. Childhood acute lymphoblastic leukemia (ALL), central nervous system (CNS) tumors, and sarcomas have been associated with elevated risks of developing symptoms of metabolic syndrome later in life [16–18]. Furthermore, previous total body irradiation has been associated with clinical manifestations of metabolic syndrome [18–20]. A healthy lifestyle and regular physical activity may efficiently reduce modifiable cardiovascular risk factors in childhood cancer survivors and the general population [21–23]. Thus, promotion of a healthy life style has been strongly advocated in this growing population at risk [21,24].

Previous studies have specifically investigated components of the metabolic syndrome after childhood cancer by examining laboratory values or clinical examination of small patient groups [16,18,25,26]. Moreover, findings from large cohorts of childhood cancer survivors on this topic have been based on questionnaires and hospital discharge diagnoses [26–29].

While features of metabolic syndrome have been studied after childhood cancer, this information remains scarce for young adulthood cancer survivors [16,19,26,30]. Our aim was to study the purchases of drugs targeting a triad of indications (hypertension, diabetes, hyperlipidemia), which may together manifest as metabolic syndrome in a nationwide population-based cohort of both childhood and young adulthood cancer patients in compared with siblings by linkage to the national drug purchase registry.

2. Subjects and methods

2.1. Data sources

2.1.1. The Finnish Cancer Registry

The Finnish Cancer Registry (FCR) has gathered information on all cancer diagnoses in Finland since 1953. The Registry offers population-based, nationwide and nearly complete data [31] (99% for solid tumors, 92% for hematological malignancies, and 100% for childhood cancers). Details such as the date of cancer diagnosis, the type of cancer, degree of malignancy, and possibly the cause and date of death can be retrieved via the FCR.

2.1.2. The Population Register Center

The Population Register Center maintains a nation-wide population register (CPR) collecting the personal identification code (PIC) and the date of emigration or death of each subject in Finland since 1967. After that, each Finnish resident has received an individual PIC, which is necessary for record linkages. Parents, siblings and children born after 1955 could be identified via linkage to the CPR.

2.1.3. The Drug Purchase Registry (DPR)

The DPR is maintained by the Social Insurance Institution (SII) and has collected information on all purchased prescription drugs since 1.1.1993. The registry offers data on all purchased refundable medications (except for over-the-counter drugs (OTCs) and medications administered in the hospital setting). The medications targeting metabolic syndrome investigated in our study all required prescription and hence, all of their purchases were recorded by the DPR. The DPR collects data such as the subjects' PIC, the date of purchase, its cost, and the package size. All medications were categorized according to Anatomical Therapeutic Chemical codes of the World Health Organization (WHO).

2.2. Patient and sibling population

From the FCR, we identified a total of 7551 early onset cancer patients (Fig. 1A) fulfilling certain inclusion criteria: younger than 35 years at cancer diagnosis; diagnosed with a primary malignant neoplasm (comprising benign central nervous system (CNS) tumors and those of undetermined malignancy), and having received the diagnosis between January 1st, 1994 and December 31st, 2004. Early onset cancer patients were categorized by age at cancer diagnosis into childhood cancer patients (aged below 20 years at cancer diagnosis) and young adult cancer patients (aged 20–34 years at cancer diagnosis) (Fig. 1A). The follow-up of cancer patients started from the date of primary cancer diagnosis.

The sibling cohort included 12,455 siblings of cancer patients without a cancer diagnosis before 35 years of age and who were born between January 1st, 1974, and December 31st, 2004. Furthermore, we divided siblings into two subcohorts depending on their age from the start of follow-up: born from the start of follow-up on January 1st 1994 and aged 20 years from the start of follow-up (1.1.1994) onwards (Fig. 1B). The follow-up of cancer patients and siblings stopped at death, diagnosis with a second or primary cancer, date of emigration or on December 31st, 2011,

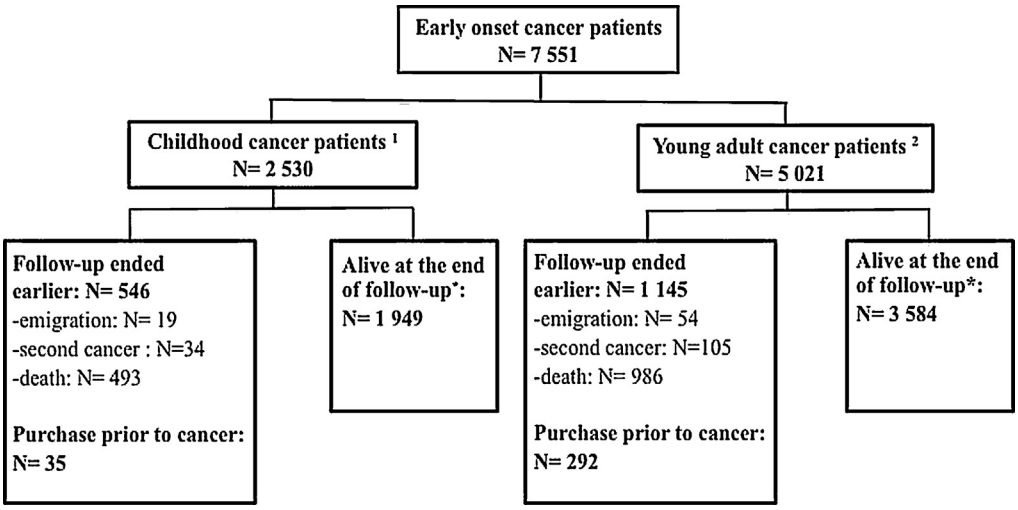

Fig. 1. (A and B) Overview of the early onset cancer (a) and sibling (b) cohort examined in our study. [1]Childhood cancer patients: aged below 20 years and [2]Young adult cancer patients aged 20–34 years at cancer diagnosis. *Follow-up ended at the latest on December 31st 2011. NA: not applicable.

Table 1
Median age (years) and range (minimum/maximum) at the end of follow-up among cancer patients, median follow-up time (years) and range, and male number (*N*)/proportion (%) by cohort.

Cohort	Median age (years)	Range (years)	Median follow-up time (years)	Range (years)	*N*/proportion(%) of male subjects
Childhood	19.2	0–37.0	10.4	0–18.0	1339 (52.9%)
YA	37.3	20.0–52.0	9.5	0–18.0	2184 (43.5%)
Younger sib	13.9	0–18.0	13.9	0–18.0	1077 (50.9%)
Older sib	29.6	20.0–38.0	9.6	0–18.0	5215 (50.5%)

whichever occurred first. Characteristics of the respective cohorts of this study are shown in Table 1.

2.3. Outcomes

2.3.1. Medications targeting metabolic syndrome

First-time purchases of the subsequent medication categories targeting the metabolic syndrome were analyzed: (1) Antihypertensives: ATC -C02–09 (including -C02 (antihypertensives), -C03 (diuretics), -C07 (beta blocking agents), -C08 (Calcium channel blockers), and -C09 (Renin-angiotensin system agents)), (2) drugs used in diabetes: ATC-A10 (ATC-A10A: Insulin and analogues and ATC-A10B: Blood glucose lowering drugs excluding insulins), and (3) lipid-lowering agents (ATC-C10), and all mentioned medication groups combined. Additionally, we investigated, if subjects purchased medications from more than one of the three main categories targeting the metabolic syndrome.

2.4. Statistical analysis

The cumulative incidence of first purchase of medication from the specific categories was assessed from the start of follow-up on January 1st, 1994 until at the latest December 31st, 2011 with death or secondary (primary in siblings) cancer as competing risks. Follow-up ended for cancer patients and siblings alike at death, primary/secondary cancer, emigration or the closing date of the study.

The hazard ratios for purchasing specific medications were evaluated in early onset cancer patients compared to siblings. Moreover, HRs were calculated for acquiring selected drugs according to selected cancer diagnoses and age at diagnosis with siblings as reference group. The HRs were computed with the Fine and Gray proportional subdistribution hazards method adjusting for birth year and age at the start of follow-up [32].

Statistical data were acquired using the software SAS for Windows version 9.3.

3. Results

3.1. Characteristics of the study populations

Our study allowed for a follow-up of maximally 18 years among a total of 7551 early onset cancer patients (2530 childhood and 5021 young adult (YA) cancer patients) and 12,455 siblings with respect to purchasing medications targeting traits of the metabolic syndrome (MetS) (Fig. 1A and B and Table 1).

3.2. Cumulative incidence of purchasing medication associated with MetS

To gain an insight on purchases of these medications over time, we analyzed the cumulative incidence of purchasing any medication for both early onset cancer patient and siblings (Fig. 2A–F). The cumulative incidence of purchasing any of the investigated drug categories rose over time in all cohorts with consistently higher values after childhood and young adult cancer than in siblings. Cumulative incidence figures varied depending on the particular medication category and the diagnostic characteristics of the cohort. Highest cumulative incidence figures and greatest differences between cancer patients and siblings were found for antihypertensives (Fig. 2A and D). Regarding the purchase of drugs used in treating diabetes, cumulative incidence values were considerably lower in all respective groups and differences were not as prominent between cancer patients and siblings (Fig. 2B and E). In contrast, the cumulative incidence of purchasing lipid-lowering medication showed a steep increase after 10 years from YA cancer diagnosis compared to siblings (Fig. 2F). The cumulative incidence of purchasing medications from one or two major drug categories remained markedly elevated after both childhood and YA cancer as compared to siblings (data not shown).

3.3. Hazard ratios for purchasing drugs associated with MetS after childhood and YA cancer compared to siblings

Furthermore, hazard ratios were assessed for purchasing drugs of particular categories in childhood and YA cancer patients compared to siblings (Table 2). The HRs for purchasing drugs from each of the three main categories were statistically significantly elevated after both childhood and YA cancer compared to siblings except for lipid-lowering drugs in childhood cancer patients (Table 2). Highest values after childhood cancer were found for purchasing antihypertensives and drugs used in diabetes (HR 4.6, 95%CI 3.1–7.0 and HR 3.0, 95%CI 1.5–6.1). The respective HRs after YA cancer were significantly elevated for purchasing antihypertensives (HR 1.5, 95%CI 1.3–1.8) and diabetes medication (HR 1.6, 95%CI 1.1–2.2) compared to siblings (Table 2). Since drugs used in diabetes comprise insulin and blood glucose lowering drugs other than insulin, we further investigated the purchases of those two subcategories. Purchases of both drug classes were more likely in childhood cancer patients than siblings (HR 5.7, 95%CI 1.5–21.1 for diabetes medication other than insulin and HR 2.7, 95%CI 1.1–6.2 for insulin), whereas among YA cancer patients only the HR for the purchase of insulin (HR 2.6, 95%CI 1.5–4.4) was higher compared to siblings. Additionally, childhood and YA cancer patients were 4.2 (95%CI 2.9–5.9) and 1.5-times more (95%CI 1.3–1.8) likely than siblings to purchase one drug from the main categories targeting the MetS. The HR value for purchasing drugs from two main categories was only increased after YA cancer (HR 1.8, 95%CI 1.1–2.8).

When examining the HRs of drug purchases with respect to the time lapse from the original cancer diagnosis, higher values were found for antihypertensives and diabetes medication after childhood cancer and also for lipid lowering agents after YA cancer especially within 3 years from cancer diagnosis (Table 2) compared with siblings.

3.4. Hazard ratios for purchasing drugs associated with MetS according to cancer diagnosis and age at cancer diagnosis

Next, the HRs for purchasing medications were examined with respect to the primary cancer diagnosis and age at diagnosis compared to siblings (Table 3A–3C). All selected childhood cancer diagnosis groups showed a greater likelihood of purchasing

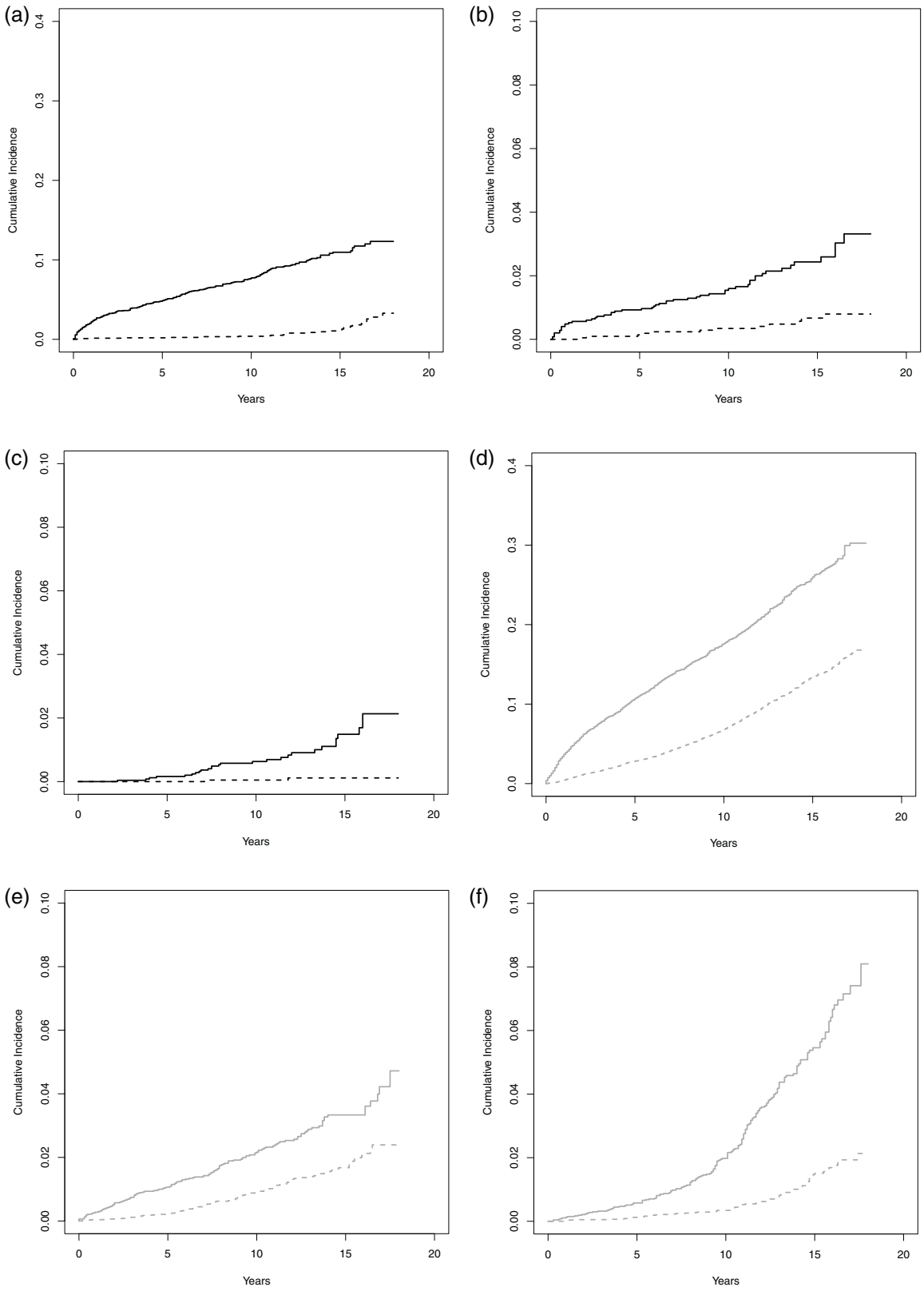

Fig. 2. (A–F) Cumulative incidence of purchasing medications which target features of metabolic syndrome after childhood (A–C) and young adult cancer (D–F) (bold line) and in siblings (dashed line) born (A–C) or aged 20 years (D–F) from the start of follow-up. Childhood cancer: (A) antihypertensive drugs, (B) medication used in diabetes, (C) lipid-lowering drugs. Young adult cancer: (D) antihypertensive drugs, (E) medication used in diabetes, (F) lipid-lowering drugs.

antihypertensives than siblings with highest values after childhood ALL and bone tumors (HR 6.1, 95%CI 3.7–10.3 and HR 4.3, 95% CI 1.9–9.4) (Table 3A). In contrast, HRs for antihypertensives among YA cancer diagnosis groups were higher only after YA ALL and acute myeloid leukemia (HR 4.8, 95%CI 3.1–7.0 and HR 3.4, 95%CI 2.2–5.1) (Table 3B).

Table 2
Hazard ratios (HRs) and 95% confidence intervals (CIs) among childhood and young adult (YA) cancer patients by the first time purchase of at least one drug from the respective drug category and time from cancer diagnosis (dg) (0–3 years and >3 years from cancer diagnosis) compared with siblings.

Cancer cohort	Drug								
	Antihypertensives			Diabetes medication			Lipid-lowering drugs		
Time from cancer dg	0–3 years	>3 years	Overall	0–3 years	>3 years	Overall	0–3 years	>3 years	Overall
Childhood cancer	14.1 (5.0–39.3)	3.3 (2.0–5.2)	4.6 (3.1–7.0)	4.9 (1.01–23.4)	2.8 (1.2–6.5)	3.0 (1.5–6.1)	NA	3.9 (0.8–18.2)	4.3 (0.9–19.5)
YA cancer	4.0 (3.0–5.2)	1.2 (0.9–1.4)	1.5 (1.3–1.8)	4.6 (2.0–11.1)	1.4 (0.9–2.2)	1.6 (1.1–2.2)	7.6 (1.8–32.8)	1.6 (0.98–2.5)	1.6 (1.0-2.5)

NA, not applicable.

Table 3A
Hazard ratios (HRs) and 95% confidence intervals (CIs) for purchasing medication targeting traits associated with metabolic syndrome by cancer diagnosis and age at diagnosis compared to siblings (childhood cancer patients).

Childhood cancer	HR (95%CI)		
Diagnosis	Diabetes	Antihypertensives	Lipid lowering drugs
ALL	6.3 (2.7–14.8)	6.1 (3.7–10.3)	8.8 (1.6–68.0)
AML	7.6 (1.9–24.5)	2.4 (0.8–6.1)	6.3 (0.3–79.1)
Bone	NA	4.3 (1.9–9.4)	NA
CNS	3.5 (1.3–9.2)	2.7 (1.5–4.9)	5.1 (0.7–44.4)
HL	3.5 (0.9–13.1)	1.8 (0.8–3.9)	3.6 (0.3–42.0)
Kidney	NA	3.8 (1.4–8.8)	NA
NBL	NA	3.9 (1.6–8.6)	NA
NHL	2.5 (0.5–9.3)	2.5 (1.1–5.2)	NA

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CNS-tumor, central nervous system tumor; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; NBL, neuroblastoma; NA, not applicable (no purchases were recorded for this medication in the particular diagnosis group).

Table 3B
Hazard ratios (HRs) and 95% confidence intervals (CIs) for purchasing medication targeting traits associated with metabolic syndrome by cancer diagnosis and age at diagnosis compared to siblings (young adult (YA) cancer patients).

Young Adult Cancer	HR (95%CI)		
Diagnosis	Diabetes	Antihypertensives	Lipid lowering drugs
ALL	3.7 (1.2–9.5)	4.8 (3.1–7.0)	1.1 (0.2–4.0)
AML	1.4. (0.3–4.6)	3.4 (2.2–5.1)	0.9 (0.2–3.0)
Bone	NA	1.6 (0.9–2.8)	1.2 (0.3–4.2)
CNS	0.7 (0.2–1.8)	1.2 (0.9–1.7)	0.5 (0.2–1.3)
HL	1.4 (0.6–3.0)	1.2 (0.9–1.7)	1.6 (0.7–3.4)
Kidney	NA	1.9 (1.0–3.3)	1.9 (0.5–6.0)
Adrenal	NA	1.7 (0.4–4.5)	NA
NHL	1.5 (0.6–3.6)	1.4 (1.0–2.0)	1.2 (0.4–3.0)

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CNS-tumor, central nervous system tumor; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; NBL, neuroblastoma; NA, not applicable (no purchases were recorded for this medication in the particular diagnosis group).

After childhood ALL, AML and CNS tumors, HRs were elevated for purchasing any diabetes medication compared to siblings (HR 6.3, 95%CI 2.7–14.8, HR 7.6, 95%CI 1.9–24.5, and HR 3.5, 95%CI 1.3–9.2) (Table 3A). Moreover, childhood ALL, AML, CNS tumor, and HL patients more likely purchased non-insulin medication than siblings with highest values after childhood leukemia (ALL: HR 23.2, 95%CI 6.4–111.2 and AML: HR 28.1, 95% 3.5–181.6) (Table 3C). Except for a higher HR value after childhood ALL (HR 3.5, 95%CI 1.1–10.2), purchases of insulins were comparable between the childhood cancer diagnostic groups and siblings. With respect to lipid-lowering medication, no differences in purchases were found compared to siblings apart from an elevated HR after childhood ALL (HR 8.8, 95%CI 1.6–68.0).

Concerning the selected YA diagnostic groups and purchases of any diabetes drug, a higher HR value was observed only after YA ALL (HR 3.7, 95%CI 1.2–9.5) (Table 3B). With respect to the specific drug classes of diabetes medication, HR values were increased only for purchasing insulin drugs after YA ALL, HL, and NHL (HR 13.6, 95%CI 4.6–36.2, HR 3.1, 95%CI 1.1–7.4, and HR 5.2, 95%CI 1.8–13.5) (Table 3C). The numbers of drug purchases and proportions by cohort and cancer diagnosis were further described in the Supplementary table.

Supplementary material related to this article found, in the online version, at http://dx.doi.org/10.1016/j.canep.2016.01.009.

4. Discussion

This study demonstrated a higher likelihood of purchasing medications targeting features of MetS in early onset cancer patients than in siblings, reflecting an increased risk for cardiovascular morbidity in this population. The purchase of medications targeting components of MetS served as a proxy for estimating the cardiovascular and metabolic morbidity after cancer at a young age compared to siblings. Both childhood and YA cancer patients were more prone to purchase antihypertensives and diabetes medication as compared to siblings. Additionally, YA cancer patients were more likely to purchase lipid-lowering drugs than siblings. Also after childhood cancer, elevated HR values were found for lipid-lowering drugs that may have possibly reached significance with a larger number of investigated subjects. Furthermore, age at cancer diagnosis and the primary site of cancer influenced the likelihood of purchasing medication associated with MetS reflecting differential risks for these adverse health outcomes.

4.1. Comparison with earlier studies

Previous studies on childhood cancer survivors have reported an elevated risk for various metabolic and endocrine disorders after cancer therapy, which may eventually contribute to the development of MetS [3,18,25,27,30,33]. Tendencies for endocrine and metabolic abnormalities have been reported in childhood CNS tumors, ALL, NHL, and HL patients [16–18,34,35]. Our study showed a markedly higher likelihood for purchasing antihypertensives in those cancer diagnostic groups compared to siblings, confirming previous reports. It must be kept in mind that the other analyzed childhood cancer diagnostic groups had similar HR values to childhood CNS-tumor patients. Moreover, we demonstrated elevated HR for the purchase of any diabetes medication after childhood ALL, AML and CNS tumors compared to siblings. Specific risk factors, such as age younger than 4 years at cancer diagnosis, cranial radiotherapy, radiation dose to the tail of the pancreas, and total body irradiation have been associated with endocrine and metabolic complications [16,18,34,36]. Our findings on elevated risk for purchasing drugs targeting the components of MetS after YA ALL, AML, HL and NHL underlined the negative impact of above mentioned cancer treatments, since TBI represents a treatment component for YA leukemias prior to hematopoietic stem cell transplantation [37]. Furthermore, vascular damage has been reported as adverse effect of chemotherapeutic agents and

Table 3C
Hazard ratios (HRs) and 95% confidence intervals (CIs) for purchasing medication targeting traits associated with metabolic syndrome by cancer diagnosis and age at diagnosis compared to siblings (purchases of diabetes medication by major category: all diabetes drugs, insulin and insulin analogues, and blood glucose lowering drugs (except insulins)).

Childhood cancer diagnosis						
Drug	ALL	AML	Bone tumor	CNS tumor	HL	NHL
Insulin	3.5 (1.1–10.2)	4.6 (0.8–19.3)	NA	0.9 (0.2–3.7)	0.7 (0.1–4.6)	1.9 (0.3–8.6)
Non-insulin	23.2 (6.4–111.2)	28.1 (3.5–181.6)	NA	18.5 (4.4–95.1)	36.1 (5.4–271.1)	NA
Any gluc-lowering	6.3 (2.7–14.8)	7.6 (1.9–24.5)	NA	3.5 (1.3–9.2)	3.5 (0.9–13.1)	2.5 (0.5–9.3)
Young adult cancer diagnosis						
Insulin	13.6 (4.2–36.2)	3.8 (0.6–15.1)	2.8 (0.1–15.0)	1.3 (0.3–4.3)	3.1 (1.1–7.4)	5.2 (1.8–13.5)
Non-insulin	NA	0.3 (0–2.0)	NA	0.4 (0.1–1.3)	0.8 (0.2–2.2)	0.6 (0.1–1.9)
Any gluc-lowering	3.7 (1.2–9.5)	1.4 (0.3–4.6)	0.7 (0–3.5)	0.7 (0.2–1.8)	1.4 (0.6–3.0)	1.5 (0.6–3.6)

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CNS-tumor, central nervous system tumor; HL, Hodgkin lymphoma; NHL, non-Hodgkin lymphoma; NBL, neuroblastoma; NA, not applicable (no purchases were recorded for this medication in the particular diagnosis group).

radiation therapy [38,39]. In our study, YA leukemia (ALL and AML) patients were more likely to purchase lipid-lowering drugs than siblings in line with the previous reports of hypertriglyceridemia and low HDL levels in childhood leukemia survivors. Our findings on elevated purchases of especially non-insulin drugs after childhood cancer mirrored an earlier investigation with similar findings on childhood cancer survivors [40].

The cumulative incidence of purchasing drugs used in MetS had a rising trend of over time in all groups, yet with distinctively higher values in the cancer patient cohorts. While age itself is a risk factor for developing MetS, the diverging trends in cumulative incidence for the specific medication purchases confirmed the additional negative impact of cancer treatment on these drug purchases [14].

4.2. Strengths and limitations

To the best of our knowledge, this study is the first to describe nationwide purchases of medication targeting MetS in early onset cancer patients compared to siblings. The large cohort study size including both childhood and young adult cancer patients and healthy siblings contributed to the strength of our study. Additionally, the recent cancer diagnosis time period from 1994 until 2004 allowed for an insight into the adverse health effects of contemporary cancer therapy regimes. The selection of this diagnostic time period allowed for a maximal follow-up of 18 years after cancer diagnosis. We were also able to demonstrate differences in drug purchases with respect to the time from cancer diagnosis. Highest HRs were found for drug purchases within three years from cancer diagnosis. Previous studies on metabolic or endocrine complications in childhood cancer survivors were limited by several factors, such as lower study population size due to medical exams [17,30]. investigation of only selected childhood cancer diagnoses [16,18], recall bias and selected respondents in questionnaires [28,29]. Investigations based on data from hospital discharge registries are likely to include the most severe cases of the diseases, as only those patients requiring hospital treatment would be recorded in the registry and thus underestimate risks in the entire cancer survivor cohort [27]. Since population-based data linkage was performed to the national drug purchase registry covering nearly all purchases of prescription medication, we were able to explore drug purchases targeting MetS among all cancer patients aged below 35 years at diagnosis and siblings. A large body of literature has addressed metabolic disorders after childhood cancer treatment, but no information is available yet on this topic in YA cancer survivors [3,18,25,27,30,33]. Our study was unique by exploring the medication purchases also after YA cancer. Furthermore, the information on drug purchases as outpatients offered a new overview into the metabolic status of early onset cancer patients during the general follow-up outside the hospital setting. The selection of a sibling cohort as reference presented a further strength of this analysis, since siblings were likely to share the same social, economic and genetic background with early onset cancer patients.

Limitations of the study include the fact that data on the specific modes of cancer treatment were not available in our study. However, standardized protocols with specific chemotherapeutic drugs and radiation amounts have been used as guidelines especially concerning the therapy of childhood cancer in Finland [41]. While our available information on drug purchases associated with MetS lacked the specific indication, particularly the prescription of blood glucose and lipid lowering drugs is strongly associated with the conditions of hyperglycemia and hyperlipidemia. Drugs used in diabetes were divided into two classes of blood glucose lowering agents: Insulin and analogues or any drugs other than Insulin. Thus, the discrimination between the two types of diabetes mellitus as indication was not possible in our study. However, it has been described that cancer therapy, such as radiation close to the pancreatic area, may lead to the development of diabetes mellitus via exocrine pancreatic destruction and requiring Insulin. Hence, this type of diabetes mellitus due to the effects of cancer treatment been classified as distinct form of diabetes mellitus apart from the classical type 1 or 2 [42]. Consequently, the lack of information on this specific indication should not strongly affect our findings in cancer patients, especially concerning the indication of glucose-lowering drugs for diabetes mellitus type 2 only [42]. Furthermore, our measured outcome was the first purchase of medication associated with MetS. Thus, we were not able to distinguish between transient and permanent treatment of health conditions. While resolving antihypertensive and diabetes-oriented therapy has been described in the first years after allogeneic stem cell transplantation, childhood cancer survivors nevertheless showed higher levels of developing long-term metabolic traits [22,26]. Moreover, the median ages at the end of follow-up were older among childhood and YA cancer patients compared with those of the corresponding sibling cohorts. The respective ages were chosen for the start of follow-up of siblings to have a possibly similar age range compared with the respective cancer cohort. Hence, the HR analyses were adjusted for age to avoid the differences in age to interfere with the interpretation of our results.

5. Conclusions

Elevated cumulative incidence and HR values for purchasing medications associated with MetS reflected the higher chance of subsequently suffering from cardiovascular late sequelae in this population at risk for premature cardiovascular death. As the

development of MetS and its consequences can be successfully prevented by changing modifiable cardiovascular risk factors, leading a healthy life-style, physical activity, and long-term medical check-ups are crucial aspects to prevent cardiovascular disease after early onset cancer [22]. Thus, adequate, risk-based, regular and life-long cardiovascular screening may reduce the threatening burden of cardiovascular disease and excess death after the initial survival of early onset cancer.

Authorship contribution statement

The study was planned by PML, NM, and AEK. JM extracted the data from various registries and performed statistical analysis after discussions with PML, AEK, NM, and the input of the authors LM, and LSJ. All authors contributed to the interpretation and pointed out issues for discussion. AEK wrote a draft of the manuscript, which was reviewed by all authors and underwent several versions of changes. All authors approved the final version of this manuscript.

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Conflict of interest

All authors have no conflicts of interest to declare.

Ethical approval

The ethical committee of the South-West Finland Hospital District Review Board approved our study protocol. Permits for registry linkage were granted by the Center for Health and Welfare (THL/1184/5.05.00/2011), the Population Register Center, and the Social Insurance Institution.

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