Original Article

Risk Factors for Cardiovascular Disease in 5-Year Survivors of Adolescent and Young Adult Cancer: A Danish Population-Based Cohort Study

Sofie de Fine Licht, PhD[1]; Maja V. Maraldo, PhD[2]; Lena Specht, DMSc[2]; Thomas T. Nielsen, MSc[1]; Jeanette F. Winther, DMSc[1,3]; and Kathrine Rugbjerg, PhD [1]

BACKGROUND: An increased risk of metabolic syndrome has been reported for childhood cancer survivors and for adult survivors with certain cancer types. One previous study reported on the risk for diseases in the metabolic syndrome specifically among survivors of adolescent and young adult cancers. **METHODS:** The study comprised 11,822 five-year survivors of adolescent and young adult cancer (ages 15-39 years at diagnosis) who were diagnosed during the period from 1994 through 2009 in Denmark and a population-based comparison cohort of 76,024 individuals. The cohorts were linked to Danish nationwide registries for information on hospital contacts and purchase of prescription drugs related to metabolic syndrome, respectively. Standardized rate ratios (RRs) for hospital contacts (SHRRs) and prescriptions (SPRRs) with 95% CIs were calculated for diabetes, hyperlipidemia, and hypertension. **RESULTS:** Survivors had increased risks for hospital contacts and prescriptions for diabetes (SHRR, 1.21; 95% CI, 1.03-1.43; SPRR, 1.08; 95% CI, 0.96-1.23), hyperlipidemia (SHRR, 1.18; 95% CI, 1.00-1.40; SPRR, 1.16; 95% CI, 1.08-1.25), and hypertension (SHRR, 1.27; 95% CI, 1.15-1.41; SPRR, 1.25; 95% CI, 1.20-1.31). The highest risks for hospitalizations were among survivors of brain cancer (RR, 2.94 for diabetes) and Hodgkin lymphoma (RR, 2.40 for diabetes). Survivors of brain cancer and Hodgkin lymphoma were most likely to purchase prescription drugs for diseases in metabolic syndrome. **CONCLUSIONS:** Survivors of adolescent and young adult cancer are at increased risk of hospital contacts and purchase of prescription drugs for diseases in metabolic syndrome. Survivors at high risk should be followed closely to improve prevention, early detection, and management of these diseases to ultimately minimize the risk of cardiovascular diseases. ***Cancer* 2020;126: 659-669**. © *2019 American Cancer Society*.

KEYWORDS: adolescents and young adults, diabetes, hyperlipidemia, hypertension, metabolic syndrome.

INTRODUCTION

Cardiac late effects in cancer survivors may arise not only from the direct toxicity of cancer treatment but also indirectly from treatment-induced changes in endocrine and metabolic functions, which may give rise to risk factors for cardiovascular diseases.[1] Cardiovascular risk factors cluster into the "metabolic syndrome," which is characterized by abdominal obesity, insulin resistance, dyslipidemia, and hypertension.[2] Increased risks for metabolic syndrome or its components have been reported in survivors of childhood cancer,[3,4] testicular cancer,[5-7] breast cancer,[8] and hematologic cancers[9] and in those who were treated with stem cell transplantation.[10] In a recent study in Finland, the purchase of drugs associated with metabolic syndrome was investigated in survivors of early-onset cancer. The study showed that cancer survivors more often purchased medication for diseases associated with metabolic syndrome than their siblings.[11] In the current study, we report on both hospital contacts and purchase of prescription drugs associated with metabolic syndrome among survivors of adolescent and young adult cancer and compare such events with those in a subset of the general population. The study period was from 1995 through 2015.

MATERIALS AND METHODS

All citizens of Denmark are assigned a unique, 10-digit, civil personal registration number at birth or immigration by the Danish Civil Registration, which also includes information on immigrations, emigrations, and death.[12] This unique number enables linkages of data held in the nationwide registries that were used in the current study, namely, the Danish Civil Registration System, the Danish National Patient Register, and the Danish National Prescription Registry.

Corresponding author: Kathrine Rugbjerg, PhD, Childhood Cancer Research Group, Danish Cancer Society Research Center, Strandboulevarden 49, Copenhagen 2100, Denmark; kathrine.rugbjerg@gmail.com

[1]Childhood Cancer Research Group, Danish Cancer Society Research Center, Copenhagen, Denmark; [2]Department of Clinical Oncology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark; [3]Department of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus, Denmark

DOI: 10.1002/cncr.32580, **Received:** May 20, 2019; **Revised:** September 4, 2019; **Accepted:** September 4, 2019, **Published online** November 12, 2019 in Wiley Online Library (wileyonlinelibrary.com)

Identification of Cohorts

The Danish Cancer Registry was initiated in 1943, and registration of cancers has been mandatory since 1987.[13] From the Danish Cancer Registry, we identified 16,162 five-year survivors of adolescent or young adult cancer (ages 15-39 years at cancer diagnosis) who were diagnosed in the period from January 1, 1994 to December 31, 2009. For each cancer survivor, 5 population-based comparison individuals of the same sex and year of birth were chosen randomly from the Danish Civil Registration System.[12] Individuals who were eligible for the comparison cohort were alive and free of cancer 5 years after the date of their corresponding survivor's cancer diagnosis. Cancer survivors who emigrated within 5 years of their cancer diagnosis, or on a corresponding date for those in the comparison cohort, were excluded.

The Danish National Patient Register

The survivor and comparison cohorts were linked to the records of the Danish National Patient Register,[14] which contains records for all admissions to public hospitals in Denmark since January 1, 1977; for each admission, a primary diagnosis and up to 19 secondary diagnoses are registered. Information on outpatient visits and contacts with private hospitals has been included since January 1, 1995 and January 1, 2002, respectively.[14] Study participants with congenital malformations or chromosome abnormalities were identified in the Patient Register and excluded because of a potential confounding association between these conditions and the outcomes of the current study (Fig. 1). Cancer survivors and individuals in the comparison cohort who had hospital contacts for diabetes, hyperlipidemia, or hypertension before their cancer diagnosis were also excluded.

The Danish National Prescription Registry

The Danish National Prescription Registry contains information on all prescription drugs dispensed to individuals at Danish community pharmacies since 1995; electronic registration is mandatory for the pharmacies.[15] For the current study, we excluded cancer survivors and individuals in the comparison cohort who had filled prescriptions for drugs against diabetes, hyperlipidemia, and hypertension before their cancer diagnosis. After these exclusions, 11,822 survivors of adolescent and young adult cancer and 76,024 individuals in the comparison cohort fulfilled the criteria for inclusion in the study (Fig. 1). Table 1 shows the characteristics of the cancer survivor cohort.

Outcomes

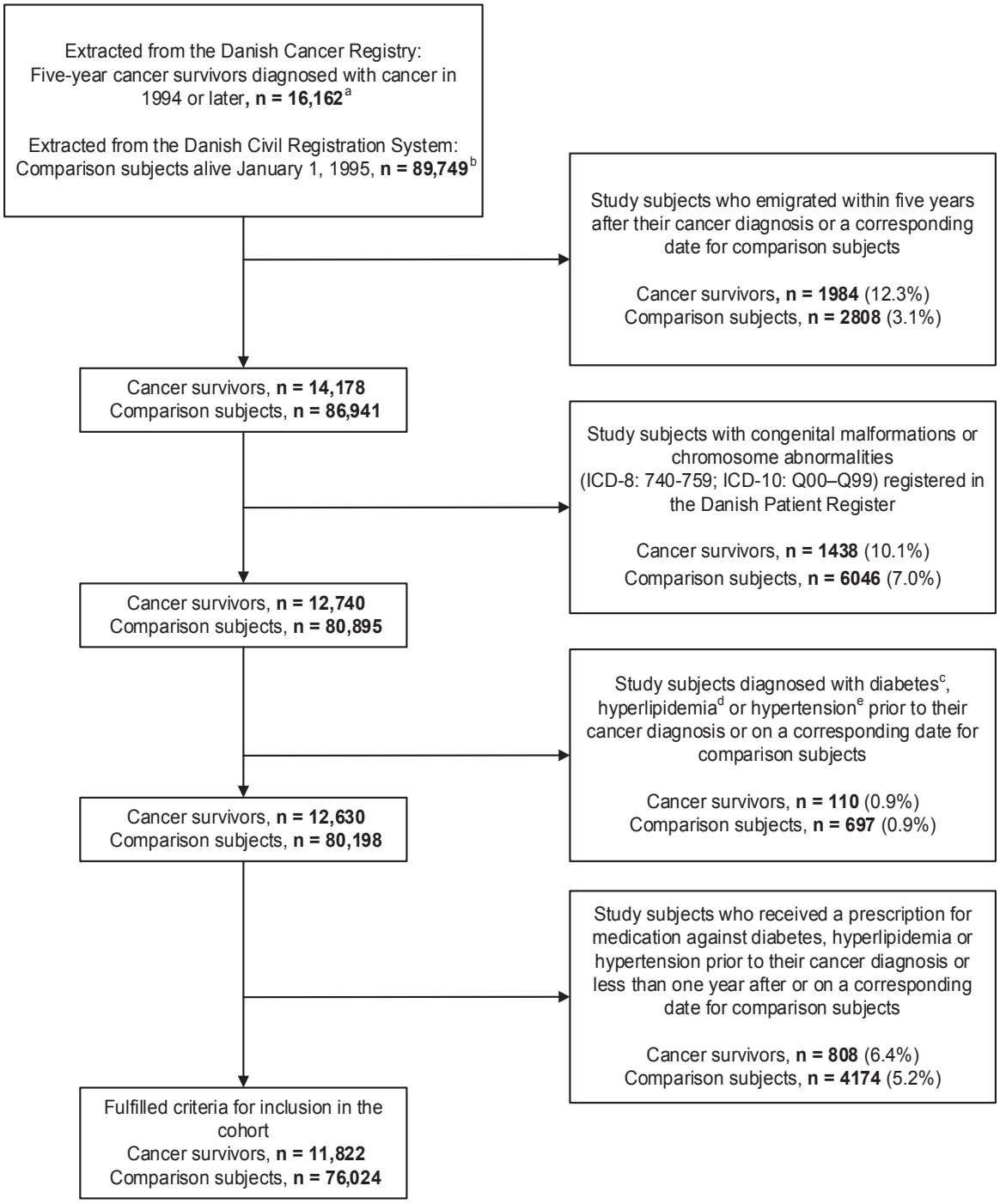
During follow-up, we identified diagnoses of diabetes, hyperlipidemia, and hypertension made at inpatient and outpatient visits to hospitals. Primary and secondary diagnoses of diabetes, hyperlipidemia, and hypertension were considered equally valid as measures of the existence of these diseases and were included in the current study. The specific diagnoses and corresponding International Classification of Diseases (ICD) codes are listed in Table 2. We sought information on prescriptions for drugs for the treatment of diabetes, hyperlipidemia, and hypertension purchased during the follow-up period. The drugs and the corresponding Anatomical Therapeutic Chemical codes are listed in Table 2.

Statistical Analyses

Follow-up started 5 years after cancer diagnosis or on the corresponding date for individuals in the comparison cohort and ended on the date of death, emigration, diagnosis of a second cancer for cancer survivors, diagnosis of a first cancer for individuals in the comparison cohort, or the end of the study on December 31, 2015, whichever came first. Rates of hospital diagnoses and purchased drugs in the cohort of survivors of adolescent and young adult cancer were compared with the age-specific, sex-specific, and calendar year-specific rates in the population-based comparison cohort. Standardized rate ratios (SRRs) were estimated by comparing the observed rate of diagnosis of 1 of the selected diseases at hospital or purchase of 1 of the selected drugs by cancer survivors (Table 2) with the expected rate, which was based on diagnoses and purchase of drugs in the comparison cohort. Corresponding 95% CIs were determined on the basis of Poisson distribution. In estimating the risks for diabetes, hyperlipidemia, and hypertension (hospital diagnosis or purchase of prescribed drug), 1 person counted only once even if they had several hospital diagnoses for 1 of the diseases. Absolute excess rates with corresponding 95% CIs were calculated as the difference between the observed rates (for survivors) and the expected rates (for the comparison cohort) per 100,000 person-years. The analyses were stratified on sex, type of cancer, age at cancer diagnosis, and attained age to evaluate the impact of these factors on the risks of diabetes, hyperlipidemia, and hypertension. Thus, the survivors included in each category of attained age were those who fulfilled the criteria for entry into the respective age categories.

RESULTS

We studied 11,822 survivors of adolescent or young adult cancer (43% men) who were diagnosed during the period from 1994 through 2009. Table 1 shows the characteristics of the cohort. The comparison cohort



[a] Survivors of cancer diagnosed at age 15−39 years in the period 1994–2009
[b] Comparison subjects were selected with replacements
[c] Diabetes: ICD-8: 249, 250; ICD-10: E10-E14
[d] Hyperlipidemia: ICD-8: 279; ICD-10: E78
[e] Hypertension: ICD-8: 400-404; ICD-10: I10-I15

Figure 1. This flow chart illustrates exclusions from the cohort of survivors of cancers diagnosed in adolescence or young adulthood and exclusions from the population-based comparison cohort. ICD-8 and ICD-10 indicate International Classification of Diseases 8th and 10th revisions, respectively.

TABLE 1. Characteristics of the Cohort of Adolescents and Young Adult 5-Year Survivors of Cancer Diagnosed at Ages 15 to 39 Years in Denmark During the Period From 1994 Through 2009

	Both Sexes		Men		Women	
Characteristic	No.	%	No.	%	No.	%
Total	11,822	100.0	5088	43.0	6734	57.0
Age at cancer diagnosis, y						
15-19	662	5.6	388	7.6	274	4.1
20-24	1163	9.8	621	12.2	542	8.0
25-29	2204	18.6	1021	20.1	1183	17.6
30-34	3395	28.7	1472	28.9	1923	28.6
35-39	4398	37.2	1586	31.2	2812	41.8
Calendar period of cancer diagnosis						
1994-1999	4533	38.3	1999	39.3	2534	37.6
2000-2004	3631	30.7	1514	29.8	2117	31.4
2005-2009	3658	30.9	1575	31.0	2083	30.9
Highest level of education achieved[a]						
Short	1731	14.6	845	16.6	886	13.2
Medium	5309	44.9	2496	49.1	2813	41.8
Long	4566	38.6	1682	33.1	2884	42.8
Unknown	216	1.8	65	1.3	151	2.2
Type of cancer[b]						
Malignant melanoma of skin	2304	19.5	730	14.3	1574	23.4
Testicular cancer	2172	18.4	2172	42.7		
Breast cancer	1441	12.2	7	0.1	1434	21.3
Cervical cancer	1356	11.5			1356	20.1
Brain cancer	812	6.9	400	7.9	412	6.1
Hodgkin lymphoma	589	5.0	335	6.6	254	3.8
Non-Hodgkin lymphoma	393	3.3	238	4.7	155	2.3
Thyroid cancer	383	3.2	83	1.6	300	4.5
Spinal cord, cranial nerves, and other and unspecified parts of the CNS	259	2.2	136	2.7	123	1.8
Cancer of other connective tissue	209	1.8	86	1.7	123	1.8
Other types of cancer[c]	1904	16.1	901	17.7	1003	14.9
Type of censoring						
Death	699	5.9	271	5.3	428	6.4
Emigration	233	2.0	137	2.7	96	1.4
Disappeared or no records in the Danish Civil Registration System	11	0.1	7	0.1	4	0.1
Diagnosis of a second cancer	491	4.2	161	3.2	330	4.9
End of follow-up (December 31, 2015)	10,388	87.9	4512	88.7	5876	87.3

Abbreviations: CNS, central nervous system; ICD-10, International Classification of Diseases, 10th revision.
[a]The highest level of education achieved in the follow-up period is shown. "Short" indicate mandatory school, corresponding to a maximum length of education of 7 years for persons born before January 1, 1958, and 9 years for persons born at or after this date; "medium" indicates secondary school and vocational education, which approximates to a maximum of 10 to 12 years of schooling; "long" indicates short-term, medium-term, or long-term higher education, approximately >12 years of education; "unknown" indicates that no records exists in the Danish education registries.
[b]The following ICD-10 codes were used: malignant melanoma of skin, C43; testicular cancer, C62; breast cancer, C50; cervical cancer, C53; brain cancer, C71, C751-C753, D330-D332, D430-D432, D352-D354, and D443-D445; Hodgkin lymphoma, C81; non-Hodgkin lymphoma, C82-C85 and C883-C889; thyroid cancer, C73; spinal cord, cranial nerves, and other and unspecified parts of the CNS, C72, D333-D339, and D433-D439; cancer of other connective tissue, C49, C461, C463, C467, C468, C469, and B210.
[c]"Other types" of cancer include all other types of cancer. The 11th to 20th most common cancers in adolescents and young adults were ovary; colon; myeloid leukemia; meninges; urinary bladder; bones, joints, and articular cartilage; rectum; lymphatic leukemia; lung, bronchus, and trachea; and kidney.

consisted of 76,024 people from the general population (44.2% men). The mean follow-up was 8.3 years (range, 0-17 years) for survivors and 8.9 years (range, 0-17 years) for the comparison cohort. Of the survivors, 38% were followed for ≥10 years, and 11% were followed for ≥15 years; the corresponding percentages for individuals in the comparison cohort were 43% and 12%, respectively.

Hospital Contacts

Survivors of adolescent and young adult cancer were at increased risk of a hospital contact for diabetes (hospital contact SRR, 1.21; 95% CI, 1.03-1.43) and hypertension (hospital contact RR, 1.27; 95% CI, 1.15-1.41) compared with individuals in the population-based comparison cohort (Table 3). The absolute excess rates indicated that survivors had 31 more hospital contacts for diabetes and 95 more hospital contacts for hypertension per 100,000 person-years than individuals in the population-based comparison cohort (data not shown). Only men had significantly increased risks of hospitalization for diabetes (RR, 1.40; 95% CI, 1.12-1.74); and, for hypertension, both men and women had significantly increased risks (men: RR, 1.41; 95% CI, 1.21-1.65; women: RR,

TABLE 2. Diagnoses and Medications Related to Risk Factors for Metabolic Syndrome; Diagnoses Listed With Codes According to the International Classification of Diseases, Versions 8 and 10, and Prescription Drugs Listed With the Codes of the Anatomical Therapeutic Chemical Classification System

Disease	Diagnosis	ICD-8 Code	ICD-10 Code
Diabetes	Insulin-dependent diabetes mellitus (type 1)	249	E10
	Noninsulin-dependent diabetes mellitus	250.00-250.08	E11
	Other types of diabetes mellitus	—	E13
	Diabetes mellitus without specification	250.09	E14
Hyperlipidemia	Hyperlipidemia	279	E78
Hypertension	Essential hypertension	401	I10
	Hypertension with heart disease	402	I11
	Hypertension with kidney disease	403	I12
	Hypertension with both heart and kidney disease	404	I13
	Secondary hypertension	400	I15

Disease	Prescription Drugs	ATC Code
Diabetes	Insulin and analogs	A10A
	Oral blood glucose-lowering drugs, including sulfonylureas	A10B
	Other drugs used in diabetes	A10X
Hyperlipidemia	Statins (CoA reductase inhibitors)	C10AA
	Combination drugs: Simvastatin and ezetimibe	C10BA02
Hypertension	Antihypertensives	C02
	Diuretics	C03
	β-Blocking agents	C07
	Angiotensin receptor blockers	C09CA
	ACE inhibitors	C09AA
	ACE inhibitors in combination with thiazide diuretics	C09DA, C09BA

Abbreviations: ACE, angiotensin-converting enzyme; ATC, Anatomical Therapeutic Chemical; CoA, coenzyme-A.

1.17; 95% CI, 1.02-1.34) (Table 3). Figure 2 shows the hospital contact SRRs (Fig. 2A-C) and the prescription SRRs (Fig. 2D,E) by years since cancer diagnosis.

Purchase of Prescription Drugs

Survivors of cancer purchased significantly more prescription drugs for hyperlipidemia (RR, 1.16) and hypertension (RR, 1.25) than individuals in the population-based comparison cohort (Table 4). Male survivors purchased more drugs for all 3 diseases than males in the population-based comparison cohort, with the highest RR for antihypertensives (RR, 1.36; 95% CI, 1.27-1.47) (Table 4). Female survivors purchased more drugs against hyperlipidemia (RR, 1.13; 95% CI, 1.02-1.26) and hypertension (RR, 1.19; 95% CI, 1.13-1.26) than females in the comparison cohort (Table 4).

Age at Cancer Diagnosis

When the cancer survivor cohort was stratified according to age at cancer diagnosis, there was a tendency toward higher RRs for hospital contacts among survivors of cancer diagnosed at the youngest ages (15-29 years at cancer diagnosis: range of RR for diabetes, 1.30-1.69; RR for hyperlipidemia, 1.51 [only 1 estimate]; range of RR for hypertension, 1.54-2.11) compared with older age groups (ages 30-39 years at cancer diagnosis: range of RR for diabetes, 1.08-1.24; range of RR for hyperlipidemia, 1.11-1.17; range of RR for hypertension, 1.11-1.33) (Table 3). Also, for the purchase of prescription drugs, we saw that survivors who were diagnosed at ages 15 to 29 years tended to have slightly higher risks (range of RR for diabetes, 0.89-1.04; range of RR for hyperlipidemia, 0.84-1.38; range of RR for hypertension, 1.16-1.35) than those diagnosed at ages 30 to 39 years (range of RR for diabetes, 1.08-1.21; range of RR for hyperlipidemia, 1.12-1.25; range of RR for hypertension, 1.12-1.30) (Table 4).

Attained Age

For cancer survivors, the RR of hospital contact for diabetes, hyperlipidemia, and hypertension was increased at attained ages between 20 and 59 years compared with individuals in the population-based comparison cohort (range of RR for diabetes, 1.04-1.75; range of RR for hyperlipidemia, 1.14-1.26; range of RR for hypertension, 1.06-2.22) (Table 3). Only a few of these risk estimates were significantly increased (Table 3). The RRs of purchasing drugs for treatment of hyperlipidemia and hypertension were increased for all attained ages (range of RR for hyperlipidemia, 1.13-2.36; range of RR for hypertension, 1.11-1.81) (Table 4). The relative risks of purchasing drugs for the treatment of diabetes were increased for survivors with attained ages from 20 to 49 years (Table 4).

TABLE 3. Standardized Hospital Contact Rate Ratios for Diabetes, Hyperlipidemia, and Hypertension According to Sex, Age at Cancer Diagnosis, and Type of Cancer in 11,822 Five-year Survivors of Cancer Diagnosed at Ages 15 to 39 Years in the Period 1994 Through 2009[a]

	Survivors		Diabetes		Hyperlipidemia		Hypertension	
Characteristic	No.	%	No. of Obs	SHRR (95% CI)	No. of Obs	SHRR (95% CI)	No. of Obs	SHRR (95% CI)
Sex								
Both sexes	11,822	100.0	173	1.21 (1.03-1.43)[b]	158	1.18 (1.00-1.40)	434	1.27 (1.15-1.41)[b]
Men	5088	43.0	96	1.40 (1.12-1.74)[b]	86	1.21 (0.96-1.52)	195	1.41 (1.21-1.65)[b]
Women	6734	57.0	77	1.04 (0.82-1.39)	72	1.15 (0.90-1.48)	239	1.17 (1.02-1.34)[b]
Age at cancer diagnosis, y								
15-19	662	5.6	7	1.69 (0.80-3.57)	—[c]	—	6	2.11 (1.00-4.46)
20-24	1163	9.8	11	1.30 (0.71-2.35)	—[c]	—	19	1.54 (0.98-2.43)
25-29	2204	18.6	31	1.45 (1.01-2.08)[b]	22	1.51 (0.99-2.32)	70	1.66 (1.31-2.12)[b]
30-34	3395	28.7	52	1.24 (0.94-1.64)	42	1.11 (0.81-1.51)	132	1.33 (1.12-1.59)[b]
35-39	4398	37.2	72	1.08 (0.85-1.37)	88	1.17 (0.94-1.45)	206	1.11 (0.97-1.28)
Attained age, y[d]								
20-29	1805	15.6	7	1.71 (0.75-3.92)	—[c]	—	6	2.22 (0.88-5.57)
30-39	6899	59.5	45	1.75 (1.26-2.44)[b]	17	1.26 (0.75-2.12)	71	1.65 (1.28-2.15)[b]
40-49	9104	78.5	91	1.09 (0.87-1.36)	88	1.14 (0.91-1.43)	251	1.28 (1.11-1.46)[b]
50-59	3325	28.7	30	1.04 (0.71-1.53)	52	1.25 (0.93-1.67)	105	1.06 (0.87-1.31)
60-69	116	1.0	—[c]	—	—[c]	—	—[c]	—
Type of cancer								
Malignant melanoma	2304	19.5	14	0.55 (0.33-0.94)[b]	16	0.70 (0.43-1.15)	54	0.87 (0.66-1.14)
Testicular cancer	2172	18.4	38	1.21 (0.88-1.67)	36	1.11 (0.80-1.55)	75	1.18 (0.94-1.49)
Breast cancer	1441	12.2	20	1.22 (0.78-1.90)	21	1.34 (0.87-2.07)	44	0.90 (0.67-1.21)
Cervical cancer	1356	11.5	6	0.36 (0.16-0.80)	19	1.32 (0.84-2.09)	45	0.95 (0.71-1.28)
Brain cancer	812	6.9	23	2.94 (1.94-4.45)[b]	6	0.91 (0.41-2.04)	33	1.99 (1.41-2.80)[b]
Hodgkin lymphoma	589	5.0	15	2.40 (1.44-4.00)[b]	9	1.76 (0.91-3.39)	31	2.51 (1.76-3.58)[b]
Non-Hodgkin lymphoma	393	3.3	—[c]	—	6	1.20 (0.54-2.69)	16	1.37 (0.84-2.24)
Thyroid cancer	383	3.2	8	1.77 (0.88-3.56)	—[c]	—	14	1.20 (0.71-2.02)
Spinal cord, cranial nerves, and CNS cancers	259	2.2	—[c]	—	—[c]	—	4	0.56 (0.21-1.49)
Cancer of other connective tissues[e]	209	1.8	—[c]	—	—[c]	—	11	2.23 (1.23-4.02)[b]
Other types of cancer[f]	1904	16.1	40	1.70 (1.24-2.33)[b]	40	1.76 (1.28-2.41)[b]	107	1.92 (1.58-2.33)[b]

Abbreviations: CNS, central nervous system; Obs, observations; SHRR, standardized hospital contact rate ratio.
[a]The comparison cohort consisted of 76,024 population-based individuals.
[b]This risk estimate significantly increased or decreased.
[c]According to the rules of Statistics Denmark, we were not allowed to report on diseases for which there were ≤2 observations. The risk estimates for diseases with ≥3 observations could have been deleted to avoid calculating observations in 1 category with a deleted number of observations.
[d]The number of survivors at entry into the category are shown.
[e]"Cancer of other connective tissues"' includes malignant neoplasms of connective and soft tissue of: the head, face, and neck (International Classification of Diseases, 10th revision code C490); upper limb, including shoulder (C491); unspecified lower limb, including hip (C492); thorax (C493); abdomen (C494); pelvis (C495); trunk, unspecified (C496); malignant neoplasms of overlapping sites of connective and soft tissue (C498); and unspecified (C499). For >50% of the 207 persons in this group, the cancer was located in the upper limb, including the shoulder, or in the lower limb, including the hip.
[f]"Other types" of cancer include all other types of cancer. The 11th to 20th most common cancers in adolescents and young adults were ovary; colon; myeloid leukemia; meninges; urinary bladder; bones, joints, and articular cartilage; rectum; lymphatic leukemia; lung, bronchus, and trachea; and kidney.

Type of Cancer: Hospital Contacts

Survivors of brain cancer and Hodgkin lymphoma had a significantly increased risk of hospitalization for diabetes and hypertension (Table 3). Increased risks of hospitalization for ≥1 of the 3 diseases were observed for all survivors of the 10 most common cancers in adolescents and young adults, except for survivors of malignant melanoma and cancer of the spinal cord, cranial nerves, or central nervous system (CNS) (Table 3). Survivors of "other types" of cancer were at significantly increased risk of hospitalization for all 3 diseases (Table 3). Among survivors with "other types" of cancer, the highest risks of hospital contact were those of survivors of kidney cancer (RR, 3.3; 95% CI, 1.8-6.1), myeloid leukemia (RR, 2.7; 95% CI, 1.6-4.6), and lymphatic leukemia (RR, 2.9; 95% CI, 1.1-5.4). Most hospital contacts by these survivors were for diabetes and hypertension (data not shown).

Type of Cancer: Purchase of Prescription Drugs

Survivors of brain cancer and "other types" of cancer were significantly more likely to purchase prescribed diabetes drugs, and survivors of testicular cancer, brain cancer, Hodgkin lymphoma, and "other types" of cancer were significantly more likely to purchase prescribed drugs for hyperlipidemia. The risk estimates for purchasing prescribed antihypertensives were increased for survivors of

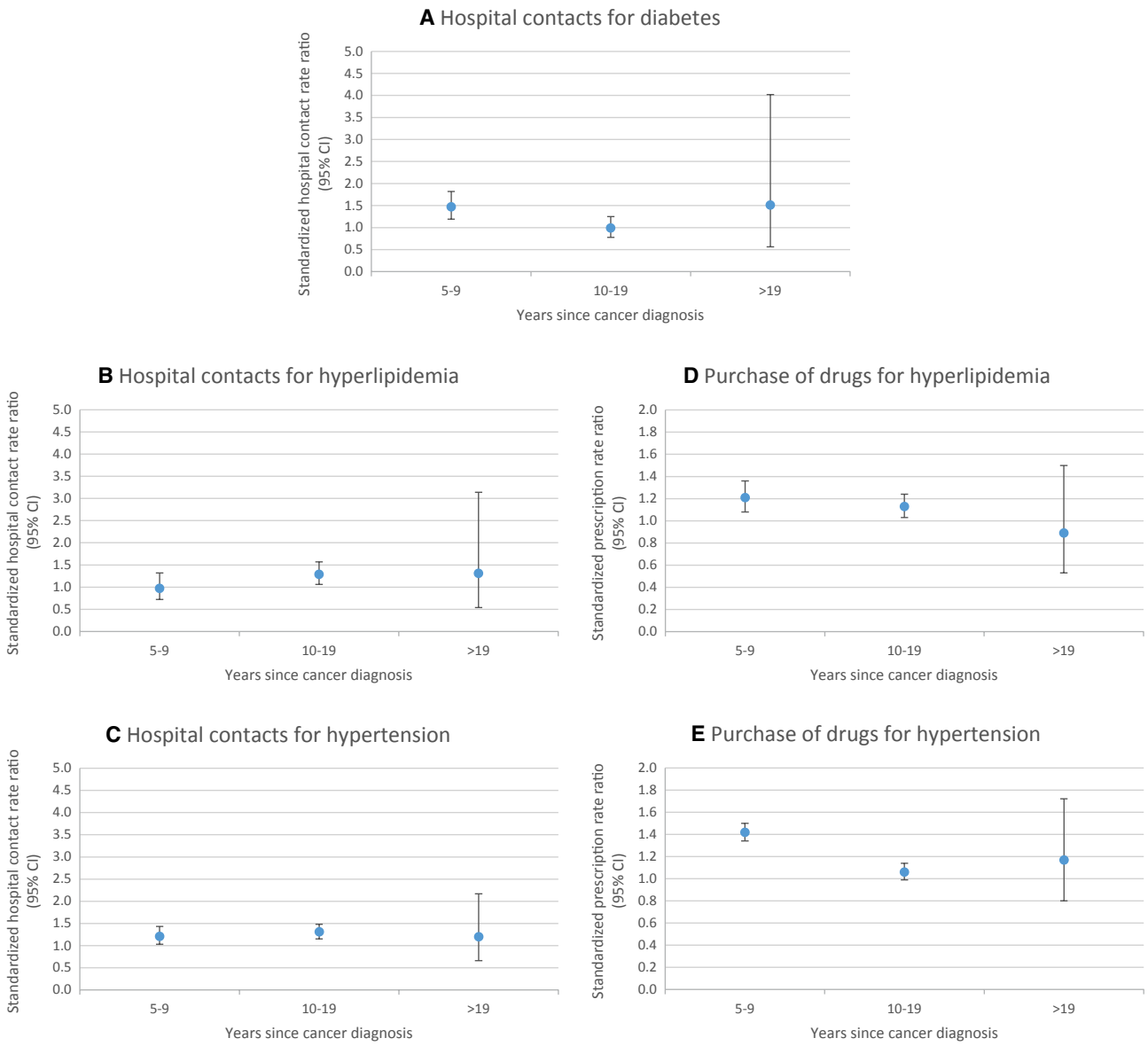


Figure 2. Charts illustrate standardized hospital contact rate ratios for (A) diabetes, (B) hyperlipidemia and (C) hypertension, and standardized rate ratios of purchased prescription drugs for (D) hyperlipidemia and (E) hypertension by years since cancer diagnosis. The rates for purchased prescription drugs for diabetes were too small to be reported.

the 10 most common cancer types, except malignant melanoma, cervical cancer, and cancer of the spinal cord, cranial nerves, and CNS. Of all prescriptions, 2221 of 3330 were for antihypertensives (Table 4). Similar to what was observed for hospital contacts, survivors of brain cancer were significantly more likely to purchase prescribed drugs for the treatment of all 3 diseases (diabetes, hyperlipidemia, and hypertension), and survivors of Hodgkin lymphoma were significantly more likely to fill prescriptions for medication against hyperlipidemia and hypertension. Survivors of testicular, breast and spinal cord, cranial nerve, or CNS cancers were more likely to have been prescribed medication against the 3 diseases, but not all estimates were significantly increased (Table 4). Survivors of "other types" of cancer were significantly more likely to purchase drugs for the treatment of all 3 diseases, with the highest RRs for survivors of lymphatic leukemia (RR, 2.7; 95% CI, 1.8-4.0), kidney cancer (RR, 2.7; 95% CI, 1.9-4.0), and myeloid leukemia (RR, 2.6; 95% CI, 1.9-3.4; data not shown). Most of the prescriptions were for antihypertensives.

TABLE 4. Standardized Prescription Rate Ratios for Drugs Against Diabetes, Hyperlipidemia, and Hypertension According to Sex, Age at Cancer Diagnosis, and Type of Cancer in 11,822 Five-Year Survivors of Cancer Diagnosed at Ages 15 to 39 Years in the Period 1994 Through 2009[a]

	Survivors		Prescriptions for Drugs Against Diabetes		Prescriptions for Drugs Against Hyperlipidemia		Prescriptions for Drugs Against Hypertension	
Characteristic	No.	%	No. of Obs	SPRR (95% CI)	No. of Obs	SPRR (95% CI)	No. of Obs	SPRR (95% CI)
Total	11,822	100.0	288	1.08 (0.96-1.23)	821	1.16 (1.08-1.25)[b]	2221	1.25 (1.20-1.31)[b]
Sex								
Men	5088	43.0	140	1.18 (0.98-1.41)	428	1.18 (1.07-1.31)[b]	844	1.36 (1.27-1.47)[b]
Women	6734	57.0	148	1.01 (0.85-1.20)	393	1.13 (1.02-1.26)[b]	1377	1.19 (1.13-1.26)[b]
Age at cancer diagnosis, y								
15-19	662	5.6	12	1.04 (0.59-1.83)	10	1.38 (0.74-2.57)	53	1.35 (1.03-1.78)[b]
20-24	1163	9.8	21	0.92 (0.60-1.41)	34	1.21 (0.86-1.70)	138	1.33 (1.12-1.57)[b]
25-29	2204	18.6	42	0.89 (0.65-1.21)	76	0.84 (0.67-1.06)	332	1.16 (1.04-1.29)[b]
30-34	3395	28.7	81	1.08 (0.86-1.35)	234	1.12 (0.98-1.28)	622	1.12 (1.03-1.21)[b]
35-39	4398	37.2	132	1.21 (1.01-1.44)[b]	467	1.25 (1.14-1.37)[b]	1076	1.30 (1.28-1.45)[b]
Attained age, y[c]								
20-29	1805	15.6	18	1.42 (0.85-2.36)	11	2.24 (1.13-4.42)[b]	81	1.81 (1.42-2.32)[b]
30-39	6899	59.5	64	1.01 (0.77-1.31)	108	1.25 (1.02-1.53)[b]	533	1.41 (1.29-1.55)[b]
40-49	9104	78.5	157	1.15 (0.97-1.36)	486	1.14 (1.03-1.25)[b]	1310	1.21 (1.14-1.28)[b]
50-59	3325	28.7	49	0.93 (0.69-1.25)	212	1.13 (0.98-1.30)	295	1.11 (0.98-1.25)
60-69	116	1.0	—[d]	—	4	2.36 (0.77-7.27)	—[d]	—
Type of cancer								
Malignant melanoma	2304	19.5	34	0.68 (0.48-0.95)[b]	100	0.80 (0.66-0.98)[b]	340	0.98 (0.88-1.09)
Testicular cancer	2172	18.4	56	1.03 (0.79-1.34)	200	1.20 (1.05-1.39)[b]	333	1.16 (1.04-1.29)[b]
Breast cancer	1441	12.2	37	1.33 (0.96-1.85)	98	1.14 (0.94-1.40)	320	1.25 (1.12-1.39)[b]
Cervical cancer	1356	11.5	22	0.70 (0.46-1.06)	80	1.00 (0.80-1.25)	272	1.02 (0.90-1.15)
Brain cancer	812	6.9	36	2.26 (1.62-3.14)[b]	58	1.68 (1.29-2.17)[b]	155	1.68 (1.44-1.97)[b]
Hodgkin lymphoma	589	5.0	12	0.92 (0.52-1.63)	48	1.78 (1.34-2.37)[b]	99	1.39 (1.14-1.70)[b]
Non-Hodgkin lymphoma	393	3.3	8	0.84 (0.42-1.68)	32	1.25 (0.88-1.77)	74	1.29 (1.02-1.62)[b]
Thyroid cancer	383	3.2	11	1.24 (0.68-2.24)	20	0.91 (0.59-1.42)	83	1.35 (1.09-1.68)[b]
Spinal cord, cranial nerves, and CNS cancers	259	2.2	—[d]	—	19	1.25 (0.80-1.96)	44	1.26 (0.93-1.69)
Cancer of other connective tissues[e]	209	1.8	—[d]	—	9	0.84 (0.43-1.61)	41	1.48 (1.09-2.02)[b]
Other types[f]	1904	16.1	62	1.41 (1.10-1.82)[b]	157	1.34 (1.14-1.57)[b]	460	1.69 (1.54-1.85)[b]

Abbreviations: CNS, central nervous system; Obs, observations; SPRR, standardized prescription rate ratio.

[a]The comparison group consisted of 76,024 population-based individuals.

[b]This risk estimate significantly increased or decreased.

[c]The number of survivors at entry into the category are shown.

[d]According to the rules of Statistics Denmark, we were not allowed to report on diseases for which there were ≤2 observations. The risk estimates for diseases with ≥3 observations could have been deleted to avoid calculating observations in 1 category with a deleted number of observations.

[e]"Cancer of other connective tissues"' includes malignant neoplasms of connective and soft tissue of: the head, face, and neck (International Classification of Diseases, 10th revision code C490); upper limb, including shoulder (C491); unspecified lower limb, including hip (C492); thorax (C493); abdomen (C494); pelvis (C495); trunk, unspecified (C496); malignant neoplasms of overlapping sites of connective and soft tissue (C498); and unspecified (C499). For >50% of the 207 persons in this group, the cancer was located in the upper limb, including the shoulder, or in the lower limb, including the hip.

[f]"Other types" of cancer include all other types of cancer. The 11th to 20th most common cancers in adolescents and young adults were ovary; colon; myeloid leukemia; meninges; urinary bladder; bones, joints, and articular cartilage; rectum; lymphatic leukemia; lung, bronchus, and trachea; and kidney.

DISCUSSION

After an average follow-up of 8 years, we observed an increased RR of a hospital contact for or purchase of prescription drugs against diabetes, hyperlipidemia, or hypertension in a Danish cohort of 11,822 five-year survivors of adolescent and young adult cancer. For all 3 components of the metabolic syndrome, the RRs for hospital contacts and purchase of prescription drugs were higher among men than among women. Survivors who were diagnosed with cancer at a young age (ages 15-29 years) tended to have higher RRs of hospital contact or purchase of prescription drugs against diabetes, hyperlipidemia, and hypertension. When we evaluated risk according to cancer type, we found that survivors of brain cancer and Hodgkin lymphoma had the highest RRs for hospital contacts and prescribed medication. In survivors of brain cancer, the increased risk may be explained by damage to the pituitary gland caused by intracranial pressure because of the tumor itself, surgery, or radiotherapy. The high risk of hospital contacts observed among survivors of Hodgkin lymphoma can be explained by the intensive, lengthy treatment of this cancer, which may have increased the risks for damage to the endocrine glands[16] and the circulatory system.[17]

When evaluating the risk of hospital contact and purchase of prescription drugs according to years since cancer diagnosis, we saw no clear trend for hospital contacts, and there was a tendency toward decreased risk with increasing number of years since cancer diagnosis for the purchase of prescription drugs.

Our results for survivors of testicular cancer (n = 2172) revealed an increased risk for hospital contact for all 3 diseases (diabetes, hyperlipidemia, and hypertension); however, none of these risk estimates were significantly increased. When considering the results for drug prescriptions, a significantly increased risk was found for the use of drugs against hyperlipidemia and hypertension among survivors of testicular cancer. In a register-based study from Utah that included 785 survivors of testicular cancer, an increased risk for a diagnosis of hypercholesterolemia was found (hazard ratio, 1.70; 95% CI, 1.19-2.41),[7] which is in accordance with the increased risk found in the current study. The study from Utah did not indicate that survivors of testicular cancer had increased risks for diabetes and hypertension.[7]

The purchase of drugs for diseases in the metabolic syndrome by survivors of young adult cancer has been evaluated in only 1 previous study.[11] That Finnish study provided risk estimates for survivors of cancers diagnosed at ages birth to 34 years, with specific risk estimates for 5021 survivors of cancer diagnosed at ages 20 to 34 years. Partly because of the difference in age groups, we were able to compare our results for only 2 cancer sites, namely, Hodgkin lymphoma and non-Hodgkin lymphoma. For Hodgkin lymphoma, our risk estimate for purchasing prescription drugs against diabetes was lower than that reported by Kero et al (RR, 0.9 vs hazard ratio, 1.4); however, neither estimate was significant. The likelihood of purchasing drugs for hyperlipidemia and hypertension was increased in both studies but was significantly increased only in the current study. For survivors of non-Hodgkin lymphoma, Kero et al[11] reported a nonsignificantly increased likelihood for purchasing medication against all 3 diseases, whereas we found that survivors of non-Hodgkin lymphoma were more likely to purchase drugs against hyperlipidemia and hypertension only, the latter being significantly increased. Factors that might explain the differences between the results of the 2 studies are the age at cancer diagnosis of the survivors (Kero et al, ages 20-34 years; current study, ages 15-39 years); furthermore, the comparison cohort was siblings in the Finnish study and population-based in the current study. Sibling comparisons are more similar to the cancer survivor regarding environment and genes than population comparisons, which are selected randomly according to year of birth and sex. An advantage of using a population-based comparison group versus a sibling comparison group is the possibility of deciding how many comparison individuals are necessary to reach the needed power. In the current study, we had 5 individuals from the population-based comparison cohort per cancer survivor, whereas Kero et al[11] included approximately 2 sibling comparisons per cancer survivor. Furthermore, the population comparisons selected for the current study had years of birth and sex similar to those of the survivor cohort.

Several reasons have been suggested for the increased risk of metabolic syndrome in survivors of cancer diagnosed at a young age. Treatment factors rather than genetic variations have been described[18]; and, in a recent review on childhood cancer survivors, the authors concluded that there is no evidence that genetic risk factors explain the increased risk of metabolic syndrome.[19] In a Norwegian study of 990 survivors of testicular cancer, treatment was related to the subsequent development of metabolic syndrome or components thereof.[20] The data, derived from questionnaires, clinical examinations, and laboratory tests, showed that survivors who received combined radiotherapy and chemotherapy (n = 34) had a higher risk of diabetes and a higher likelihood of using lipid-lowering medication and antihypertensives than survivors who underwent surgery, received chemotherapy only, or received radiotherapy only.[20] This result is in accordance with our finding of high risks for the components of metabolic syndrome in survivors of cancer who are typically treated intensively with both chemotherapy and radiotherapy, such as Hodgkin lymphoma. Chemotherapy, radiotherapy, and surgery can all cause endocrine disturbances, such as growth hormone deficiency, pancreatic damage, hypogonadism, and hypothyroidism, which increase the risk for developing the metabolic syndrome.[16] In a recent study, we found that survivors of Hodgkin lymphoma who were diagnosed during adolescence and young adulthood had a highly increased risk for hypothyroidism (RR, 14.9; 95% CI, 11.9-18.6),[21] likely because of the exposure of the thyroid gland to radiation. It has been suggested that both hypothyroidism and hyperthyroidism can induce insulin resistance,[22] thus the increased risk for hypothyroidism in survivors of Hodgkin lymphoma may contribute to the development of the metabolic syndrome.

Because the metabolic syndrome and cancer share risk factors (age, obesity, unhealthy diet, alcohol, and smoking), the "common soil" hypothesis proposes that metabolic syndrome is a marker for dietary risk factors that increase the risk of cancer.[23] Therefore, the observed increased risks for components of the metabolic

syndrome would be because of the people's lifestyle before the cancer diagnosis rather than, or in combination with, the cancer and its treatment. Because we excluded individuals who had hospital contacts or who purchased drugs for the treatment of components of the metabolic syndrome before their cancer diagnosis, lifestyle before cancer diagnosis is not likely to be the explanation for the observed increased risks for components of the metabolic syndrome. Furthermore, we studied survivors of cancer diagnosed in adolescence and young adulthood, thus the length of exposure to potential risk factors for cancer was very limited.

Strengths

The current study was based on unique and objective data held in the nationwide Danish registries, including both inpatient and outpatient hospital contacts and purchase of prescription drugs, with complete follow-up for a large cohort of 5-year survivors of adolescent and young adult cancer. Participation in the study was completely independent from the severity of the survivors' disease, their surplus energy, and their desire to participate in the study. By combining information on hospital contacts and prescription drugs, our results show the impacts of diabetes, hyperlipidemia, and hypertension, both at early stages, when the diseases can be treated in primary health care, and at more advanced stages, requiring hospital contact. The current study is the first to our knowledge reporting on risks for components of the metabolic syndrome with a specific focus on survivors of cancer diagnosed in adolescence and young adulthood. Thus, our results will contribute to the growing evidence on outcomes for these survivors.

Limitations

Survivors of adolescent and young adult cancer might be subject to more intensive surveillance because of more frequent contact with physicians during follow-up. This could have led to overestimation of the reported risk estimates, but not to an extent that is judged to affect the conclusions of this study. Contrary to studies in which the survivors are recruited for clinical examinations, we had no information on the exact indication for medical treatment. In studies that include clinical examinations and measurements, it is possible to have important details about the patient (indications for use of medicine, severity of the disease, time for first symptoms, smoking, physical activity, and obesity), but these details are usually unavailable in registry-based studies. In the current study, data on specific cancer treatments were not available.

Conclusions

Survivors of adolescent and young adult cancer are at higher risks of hospital contacts and purchase of prescription drugs related to diabetes, hyperlipidemia, and hypertension than individuals in the general population. The results of this study show that the groups at highest risk are men, survivors of cancer diagnosed at younger ages (15-29 years), and survivors of brain cancer and Hodgkin lymphoma. The combination of data on hospital contacts and purchase of prescription drugs allowed us to draw a detailed picture of the cardiovascular risk factors encountered by survivors of adolescent and young adult cancer. This valuable knowledge will be used to design follow-up care of survivors of these cancers and, ultimately, to prevent, postpone, or minimize cardiac late effects in this specific group of cancer survivors.

FUNDING SUPPORT

This project was funded by The Danish Council for Independent Research (grant DFF-1333-00112B).

CONFLICT OF INTEREST DISCLOSURES

Sofie de Fine Licht is currently an employee of AstraZeneca. Lena Specht reports personal fees from Takeda, Merck Sharpe & Dohme, and Kyowa Kirin and other support from Merck Darmstadt, Varian, and ViewRay outside the submitted work. The remaining authors made no disclosures.

AUTHOR CONTRIBUTIONS

Sofie de Fine Licht: wrote the article, interpreted the results, and reviewed and approved the final article. **Kathrine Rugbjerg:** Conceived the study, wrote the article, interpreted the results, and reviewed and approved the final article. **Thomas T. Nielsen:** Did the statistical analyses and reviewed and approved the final article. **Maja V. Maraldo**, **Lena Specht**, and **Jeanette F. Winther:** Helped with interpretation of the results and reviewed and approved the final article.

REFERENCES

1. de Haas EC, Oosting SF, Lefrandt JD, Wolffenbuttel BH, Sleijfer DT, Gietema JA. The metabolic syndrome in cancer survivors. *Lancet Oncol*. 2010;11:193-203.
2. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation*. 2005;112:2735-2752.
3. Pluimakers VG, van Waas M, Neggers S, van den Heuvel-Eibrink MM. Metabolic syndrome as cardiovascular risk factor in childhood cancer survivors. *Crit Rev Oncol Hematol*. 2019;133:129-141.
4. van Waas M, Neggers SJ, van der Lelij AJ, Pieters R, van den Heuvel-Eibrink MM. The metabolic syndrome in adult survivors of childhood cancer, a review. *J Pediatr Hematol Oncol*. 2010;32:171-179.
5. Haugnes HS, Aass N, Fossa SD, et al. Components of the metabolic syndrome in long-term survivors of testicular cancer. *Ann Oncol*. 2007;18:241-248.
6. Willemse PM, Burggraaf J, Hamdy NA, et al. Prevalence of the metabolic syndrome and cardiovascular disease risk in chemotherapy-treated testicular germ cell tumour survivors. *Br J Cancer*. 2013;109:60-67.
7. Hashibe M, Abdelaziz S, Al-Temimi M, et al. Long-term health effects among testicular cancer survivors. *J Cancer Surviv*. 2016;10:1051-1057.

8. Thomson CA, Thompson PA, Wright-Bea J, Nardi E, Frey GR, Stopeck A. Metabolic syndrome and elevated C-reactive protein in breast cancer survivors on adjuvant hormone therapy. *J Womens Health (Larchmt)*. 2009;18:2041-2047.
9. Li C, Liu P, Liu L, et al. Metabolic syndrome in hematologic malignancies survivors: a meta-analysis. *Med Oncol*. 2015;32:422.
10. Armenian SH, Sun CL, Vase T, et al. Cardiovascular risk factors in hematopoietic cell transplantation survivors: role in development of subsequent cardiovascular disease. *Blood*. 2012;120:4505-4512.
11. Kero AE, Madanat-Harjuoja LM, Jarvela LS, Malila N, Matomaki J, Lahteenmaki PM. Health conditions associated with metabolic syndrome after cancer at a young age: a nationwide register-based study. *Cancer Epidemiol*. 2016;41:42-49.
12. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol*. 2014;29:541-549.
13. Gjerstorff ML. The Danish Cancer Registry. *Scand J Public Health*. 2011;39(7 suppl):42-45.
14. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol*. 2015;7:449-490.
15. Pottegard A, Schmidt SAJ, Wallach-Kildemoes H, Sorensen HT, Hallas J, Schmidt M. Data resource profile: the Danish National Prescription Registry. *Int J Epidemiol*. 2017;46:798-798f.
16. Chemaitilly W, Cohen LE, Mostoufi-Moab S, et al. Endocrine late effects in childhood cancer survivors. *J Clin Oncol*. 2018;36:2153-2159.
17. Rugbjerg K, Mellemkjaer L, Boice JD, Kober L, Ewertz M, Olsen JH. Cardiovascular disease in survivors of adolescent and young adult cancer: a Danish cohort study, 1943-2009. *J Natl Cancer Inst*. 2014;106:dju110.
18. van Waas M, Neggers SJ, Uitterlinden AG, et al. Treatment factors rather than genetic variation determine metabolic syndrome in childhood cancer survivors. *Eur J Cancer*. 2013;43:668-675.
19. Clemens E, van der Kooi ALF, Broer L, et al. The influence of genetic variation on late toxicities in childhood cancer survivors: a review. *Crit Rev Oncol Hematol*. 2018;126:154-167.
20. Haugnes HS, Wethal T, Aass N, et al. Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: a 20-year follow-up study. *J Clin Oncol*. 2010;28:4649-4657.
21. Jensen MV, Rugbjerg K, de Fine Licht S, et al. Endocrine late effects in survivors of cancer in adolescence and young adulthood: a Danish population-based cohort study. *JAMA Netw Open*. 2018;1:e180349.
22. Iwen KA, Schroder E, Brabant G. Thyroid hormones and the metabolic syndrome. *Eur Thyroid J*. 2013;2:83-92.
23. Bellastella G, Scappaticcio L, Esposito K, Giugliano D, Maiorino MI. Metabolic syndrome and cancer: "the common soil hypothesis." *Diabetes Res Clin Pract*. 2018;143:389-397.