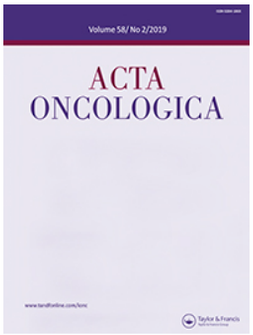

Acta Oncologica

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: https://www.tandfonline.com/loi/ionc20

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To cite this article: Camilla T. Clausen, Henrik Hasle, Anna S. Holmqvist, Laura Madanat-Harjuoja, Laufey Tryggvadottir, Finn Wesenberg, Andrea Bautz, Jeanette F. Winther & Sofie de Fine Lichton behalf of the ALiCCS study group (2019) Hyperthyroidism as a late effect in childhood cancer survivors - an Adult Life after Childhood Cancer in Scandinavia (ALiCCS) study, Acta Oncologica, 58:2, 227-231, DOI: 10.1080/0284186X.2018.1535187

To link to this article: https://doi.org/10.1080/0284186X.2018.1535187

Published online: 26 Dec 2018.

ACTA ONCOLOGICA
2019, VOL. 58, NO. 2, 227–231
https://doi.org/10.1080/0284186X.2018.1535187

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ORIGINAL ARTICLE

Hyperthyroidism as a late effect in childhood cancer survivors - an Adult Life after Childhood Cancer in Scandinavia (ALiCCS) study

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ABSTRACT

Background: Hyperthyroidism is a rare disorder which may negatively affect health and quality of life. Its occurrence in childhood cancer survivors has not previously been investigated in detail.

Material and methods: In the hospital registers of the five Nordic countries, 32,944 childhood cancer survivors and 212,675 population comparisons were followed for the diagnosis of hyperthyroidism. Hospitalisation rates, standardised hospitalisation rate ratios and absolute excess risks were calculated with 95% confidence intervals (CI).

Results: Hyperthyroidism was diagnosed in 131 childhood cancer survivors, yielding an overall relative risk of 1.6 (95% CI: 1.3–1.9) compared with population comparisons. The risk was greatest 1–5 years after the diagnosis of cancer and in survivors of thyroid cancers, neuroblastomas, acute lymphoblastic leukaemia and Hodgkin lymphoma. Sixty-seven percent of survivors with hyperthyroidism had tumours located in the head, neck or upper body and half of survivors with hyperthyroidism were irradiated with 77% of them in the head and neck area.

Conclusion: Childhood cancer survivors are at an increased risk of hyperthyroidism, potentially resulting in non-endocrine morbidity.

ARTICLE HISTORY
Received 28 June 2018
Accepted 6 October 2018

Introduction

Childhood cancer survivors often have abnormalities of the thyroid gland. These include the most common, hypothyroidism, but also thyroid carcinomas, autoimmune thyroid disorders and hyperthyroidism [1]. Thyroid complications occur primarily in patients treated with radiation to the thyroid gland or the hypothalamic-pituitary axis [2]. Chemotherapy alone has not been shown to increase the risk of thyroid dysfunction [1], but studies suggest a sensitising effect [3,4]. The Childhood Cancer Survivor Study (CCSS) and the Adult Life after Childhood Cancer in Scandinavia (ALiCCS) study both identified increased risks of hyperthyroidism in childhood cancer survivors [5–8]. The aim of this study was to look further into these findings by obtaining more thorough information on those survivors who develop hyperthyroidism using the population-based ALiCCS cohort large enough to investigate rarely, but potentially severe late effects. To the best of our knowledge, this is the first detailed study of hyperthyroidism in childhood cancer survivors. It will add to the knowledge on treatment-related risk factors for hyperthyroidism, which will be useful for guiding those clinicians being responsible for long-term follow-up care of survivors to identify high-risk patients.

Material and methods

As described previously in greater detail [9], the ALiCCS cohort consists of 43,909 individuals registered with cancer before 20 years of age in the national cancer registries of Denmark, Finland, Iceland, Norway and Sweden between the start of the cancer registries in the 1940s and 1950s and 31 December 2008. The Nordic cancer registries are nationwide and with virtually 100% coverage [10–13]. From the registries, we obtained information on the type of cancer and date of diagnosis, and patients were assigned to the 12 main diagnostic groups of the International Classification Scheme for Childhood Cancer with lymphoma further divided into Hodgkin and Non-Hodgkin lymphomas [14]. Since the start

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of centralised civil registration in the Nordic countries, all residents have been assigned a unique personal identification number, which allows accurate linkage of information among registries.

For comparison, we randomly selected 219,131 individuals of the same sex, age and country in the national population registries, referred to as population comparisons. Information on vital status and migration during follow-up was collected from the population registers for both patients and population comparisons.

Before linkage of study subjects to the respective national hospital registers, we excluded those in whom more than one primary cancer had been diagnosed in childhood, those who had died or emigrated before the start of the national hospital registers, those who had died or were censored during the first year after the date of cancer diagnosis or an equivalent time lag for the comparison subjects, those with a diagnosis of a chromosome abnormality and those with a hospital contact for hyperthyroidism before the date of cancer diagnosis or the equivalent date for comparisons. These exclusions resulted in a cohort of 32,944 1-year survivors and 212,675 population comparisons.

The nationwide hospital registers contain information on virtually all non-psychiatric hospital admissions in the five countries [15,16]. Using the unique personal identification number assigned to all citizens of the Nordic countries, we followed survivors and comparisons in the hospital registers for a primary or supplementary discharge diagnosis of hyperthyroidism (ICD-7: 252, ICD-8: 242, ICD-9: 242 and ICD-10: E05). We also included hospital-based outpatient visits in Denmark since 1995 and in Sweden since 2001.

Information on cancer treatment was abstracted from the medical records of the Danish survivors with hyperthyroidism ($n = 43$) diagnosed with cancer in 1970–2008, of which we received complete records for 28 patients. For 15 patients, we were unable to collect substantial treatment information from medical records either because the old records were lost in the hospitals, destroyed, or did not include complete information on treatment. To validate the discharge diagnosis of hyperthyroidism, we obtained information on prescriptions for thyroid and anti-thyroid hormones in 1995–2010 from the Danish Prescription Register for a sub-cohort of 34 Danish childhood cancer survivors with hyperthyroidism. Anti-thyroid medication included all pharmaceutical groups within ATC code H03B; i.e., thiouracils, sulfur-containing imidazole derivatives, perchlorates and other anti-thyroid preparations. Thyroid medications included prescriptions with all thyroid preparations (ATC code H03B).

Statistical analysis

Follow-up for hyperthyroidism began one year after the date of cancer diagnosis (and the corresponding date for population comparisons) or at the start of the hospital registers, whichever occurred first. We compared the number of first hospital contacts with hyperthyroidism in childhood cancer survivors with the expected numbers derived from the appropriate country, sex, age and calender-period specific hospitalisation rates of the population comparisons. Hospitalisation rates and standardised hospitalisation rate ratios (RRs) were calculated with 95% confidence intervals (CIs). Absolute excess risks (AERs) were derived as the difference between observed and expected rates of hospitalisation of survivors per 100,000 person-years, with corresponding 95% CIs.

Results

The 32,944 1-year survivors of childhood cancer were followed in the national hospital registers for 435,103 person-years, during which time 131 survivors had at least one hospital contact for hyperthyroidism; as 83 would have been expected, the RR was 1.57 (95% CI: 1.30–1.90), and the overall AER was 11 (6–16) per 100,000 person-years (Table 1). Thus, following 1,000 survivors for a decade would result in one new excess hospital contact with hyperthyroidism.

The RR was 1.4 for women (95% CI: 1.2–1.8) and 2.3 for men (95% CI: 1.6–3.4), which resulted in an AER of 14 (4–23) per 100,000 person-years for women and 8 (3–13) per 100,000 person-years for men. The highest risks for hyperthyroidism were those of survivors of thyroid cancer (RR =3.9; 95% CI: 2.4–6.4), neuroblastoma (RR =2.4; 95% CI: 1.0–5.8), Hodgkin lymphoma (RR =2.4; 95% CI: 1.4–4.0) and acute lymphoblastic leukaemia (ALL) (RR =2.3; 95% CI: 1.4–3.8). Of the 131 survivors who developed hyperthyroidism, 91 had had a solid tumour in childhood. Topographic information from the cancer registries showed that 67% of these survivors had tumours located in the head, neck or upper body, 22% in the mid- and lower body and 8% in the extremities; 3% were of unknown topography. The risk for hyperthyroidism was highest 1–5 years after diagnosis of childhood cancer (RR =5.5; 95% CI: 3.5–8.6) (Table 1). In survivors of ALL, central nervous system (CNS) tumours and thyroid carcinoma, the risk was also highest in the first years after the cancer diagnosis, whereas the risk of survivors of Hodgkin lymphoma was highest 5–9 years and 10–19 years after diagnosis (Table 2).

Of the 28 Danish survivors with hyperthyroidism for whom information on cancer treatment was available, 25 had undergone surgery, and all six survivors of thyroid cancer had undergone partial or full thyroidectomy (Table 3). Ten of the 13 survivors (77%) who received radiotherapy were irradiated in the head-and-neck area, and five survivors were treated in multiple areas for metastatic cancer. The radiation doses ranged from 12.5 Gy to 74 Gy, with a median total dose of 46.4 Gy to the head, neck and upper body (data not shown).

In the Danish Prescription Register, we found that 30 of 34 patients with a hospital contact for hyperthyroidism in the Danish Hospital Register were also prescribed anti-thyroid drugs, confirming the diagnosis of hyperthyroidism.

Discussion

Overall, one-year survivors of childhood cancer were found to be at a 1.6-fold increase in risk for hyperthyroidism,

TABLE 1. Observed and expected numbers of first hospital contacts for hyperthyroidism in 32,944 1-year survivors of childhood cancer in the Nordic countries.

		First hospital contacts (*n*)			Hospitalisation rate[a]		
	1-year survivors (*n*)	Observed	Expected	RR (95% CI)	Observed	Expected	AER[a] (95% CI)
Total	32 944	131	83.3	1.57 (1.30–1.90)	30.2	19.2	11 (6–16)
Sex							
Female	15 348	98	68.9	1.4 (1.2–1.8)	47.3	33.2	14 (4–24)
Male	17 596	33	14.5	2.3 (1.6–3.4)	14.5	6.4	8 (3–13)
Age at cancer diagnosis (years)							
0–4	10 029	23	16.2	1.4 (0.9–2.2)	17.3	12.1	5 (–2 to 12)
5–9	5 827	19	11.7	1.6 (1.0–2.6)	25.3	15.6	10 (–2 to 21)
10–14	6 450	27	18.8	1.4 (1.0–2.1)	31.3	21.9	9 (–2 to 21)
15–19	10 638	62	36.6	1.7 (1.3–2.2)	44.4	26.2	18 (7–29)
Time since cancer diagnosis (years)							
1–5	24 982	22	4.0	5.5 (3.5–8.6)	27.2	4.9	22 (11–34)
6–9	20 637	19	7.6	2.5 (1.6–4.0)	22.5	9.0	13 (3–24)
10–19	18 475	34	22.4	1.5 (1.1–2.1)	26.5	17.5	9 (0–18)
≥20	13 988	56	49.3	1.1 (0.9–1.5)	39.9	35.1	5 (–6 to 15)
Age at hospital contact with hyperthyroidism (attained age)							
0–9	11 510	7	0.2	47.3 (5.9–381.0)	15.7	0.3	15 (4–27)
10–19	21 630	14	6.2	2.3 (1.2–4.1)	13.0	5.8	7 (0–14)
20–29	19 072	46	22.2	2.1 (1.5–2.9]	35.8	17.2	19 (8–29)
30–39	12 265	26	23.7	1.1 (0.7–1.7)	31.8	28.9	3 (–10 to 16)
40–49	6 972	11	14.8	0.7 (0.4–1.4)	24.6	33.2	–9 (–24 to 7)
50–59	3 348	19	10.8	1.8 (1.1–2.9)	93.5	52.3	41 (–3 to 84)
≥60	1 313	8	5.7	1.4 (0.7–3.0)	118.8	84.0	35 (–52 to 122)
Type of cancer							
Leukaemia (all combined)	6 926	21	8.8	2.4 (1.6–3.7)	29.5	12.3	17 (5–30)
ALL	5 568	16	6.9	2.3 (1.4–3.8)	26.8	11.6	15 (2–28)
Lymphoma	4 504	19	10.3	1.9 (1.2–2.9)	31.8	17.2	15 (0–29)
Hodgkin lymphoma	2 453	15	6.3	2.4 (1.4–4.0)	46.5	19.4	27 (4–51)
Non-Hodgkin lymphoma	1 803	4	3.5	1.1 (0.4–3.1)	16.8	14.8	2 (–14 to 19)
CNS tumours	7 922	30	21.0	1.4 (1.0–2.1)	27.8	19.5	8 (–2 to 18)
Neuroblastomas	1 318	5	2.1	2.4 (1.0–5.8)	30.9	12.8	18 (–9 to 45)
Retinoblastomas	822	2	2.8	0.7 (0.2–2.9)	12.6	17.8	–5 (–23 to 12)
Renal tumours	1 409	2	3.1	0.6 (0.2–2.6)	9.1	14.0	–5 (–18 to 8)
Hepatic tumours	241	0	0.2	NA	NA	NA	NA
Malignant bone tumours	1 533	6	3.8	1.6 (0.7–3.5)	33.3	21.1	12 (–15 to 39)
Soft-tissue sarcomas	1 995	5	6.0	0.8 (0.4–2.0)	18.1	21.6	–3 (–19 to 12)
Germ-cell tumours	2 124	8	6.0	1.3 (0.7–2.7)	27.9	21.1	7 (–13 to 26)
Carcinomas	3 679	32	18.1	1.8 (1.2–2.5)	54.0	30.6	23 (5 to 42)
Thyroid carcinomas	848	16	4	3.9 (2.4–6.4)	116.1	29.9	86 (29–143)
Other and unspec. cancers	471	1	1.2	0.9 (0.1–6.1)	17.5	20.4	–3 (–37 to 31)

RR: standardised hospitalisation rate ratio; AER: absolute excess risk; CI: confidence interval; ALL: acute lymphoblastic leukaemia; CNS: central nervous system.
[a]Per 100,000 person-years.

compared with population comparison subjects. The highest risks were seen 1–5 years after cancer treatment and in survivors of thyroid cancers, neuroblastomas, ALL and Hodgkin lymphoma. Both the distribution of malignancies among survivors with hyperthyroidism and the received cancer treatment, suggest that hyperthyroidism occurs as a result of damage to the thyroid gland and/or the hypothalamic-pituitary axis.

The increased risk of survivors of childhood cancer for hyperthyroidism has been addressed in only a few studies. Most reported a few cases of hyperthyroidism, without further details [17–19]. However, three CCSS studies have compared the risk of hyperthyroidism in childhood cancer survivors to that of their siblings [6–8]. The results were similar to ours for childhood cancer survivors overall (1.6 in our study, 2.5 in CCSS based on 290 cases) and for survivors of ALL (2.3 in our study, 2.0 in CCSS) [7,8], but there was a striking difference in the results for survivors of Hodgkin lymphoma (2.4 in our study, 8.0 in CCSS), which may reflect differences in radiation practice [6,20]. All three CCSS studies showed that hyperthyroidism was associated with radiotherapy. For childhood cancer survivors overall, the risk for hyperthyroidism increased with the total irradiation dose [8]. For survivors of Hodgkin lymphoma, those treated with ≥35 Gy to the thyroid gland were at highest risk [6]; for survivors of ALL, those treated with craniospinal irradiation or ≥20 Gy to the pituitary gland combined with ≥15 Gy to the thyroid gland were at higher risk for hyperthyroidism than survivors treated with chemotherapy only [7]. Autoimmune thyroid disorders leading to hyperthyroidism have been reported in childhood cancer survivors undergoing stem-cell transplantation, probably due to adoptive transfer of abnormal clones of T or B cells from donor to the patient [21–23].

This study is the first comprehensive study on hyperthyroidism after childhood cancer. It included all Nordic childhood cancer survivors and all types of cancers and is based on medically verified diagnoses of hyperthyroidism registered by treating physicians. Further strengths include

TABLE 2. Observed and expected numbers of first hospital contacts for hyperthyroidism by time since diagnosis of selected cancers.

			First hospital contacts (*n*)			Hospitalisation rate[b]		
	1-year survivors (*n*)	Person-years at risk[a]	Observed	Expected	RR (95% CI)	Observed	Expected	AER (95% CI)[b]
ALL	5 568	59 899	16	7.0	2.3 (1.4–3.8)	26.7	11.6	15 (2–28)
1–5	4 734	15 195	2	0.3	6.4 (1.6–25.9)	13.2	2.1	11 (–7 to 29)
6–9	3 580	14 680	4	0.8	5.3 (2.0–14.2)	27.3	5.2	22 (–5 to 49)
10–19	2 909	19 635	6	2.5	2.4 (1.1–5.3)	30.6	12.8	18 (–7 to 42)
≥20	1 647	10 314	4	3.4	1.2 (0.5–3.2)	38.8	32.5	6 (–32 to 44)
Hodgkin lymphoma	2 453	32 324	15	6.3	2.4 (1.4–4.0)	46.4	19.4	27 (3–51)
1–5	1 898	6 455	1	0.6	1.8 (0.3–13.1)	15.5	8.5	7 (–23 to 37)
6–9	1 709	6 941	3	1.0	3.2 (1.0–9.8)	43.2	13.7	30 (–19 to 78)
10–19	1 501	10 045	6	2.2	2.7 (1.2–6.1)	59.7	22.0	38 (–10 to 86)
≥20	900	8 795	5	2.6	2.0 (0.8–4.7)	56.9	29.1	28 (–22 to 78)
CNS tumours	7 922	108 244	30	21.0	1.4 (1.0–2.1)	27.7	19.4	8 (–2 to 18)
1–5	5 957	19 400	9	1.0	9.5 (4.9–18.6)	464	4.9	42 (11–72)
6–9	5 054	20 742	1	1.8	0.6 (0.1–3.9)	4.8	8.8	–4 (–14 to 6)
10–19	4 544	31 731	6	5.6	1.1 (0.5–2.4)	18.9	17.6	1 (–14 to 16)
≥20	3 182	36 129	14	12.7	1.1 (0.7–1.9)	38.8	35.0	4 (–17 to 24)
Thyroid carcinomas	848	13 847	16	4.0	3.9 (2.4–6.4)	115.6	29.8	86 (29–142)
1–5	591	2 076	2	0.3	8.0 (2.0–32.1)	96.3	12.0	84 (–49 to 218)
6–9	595	2 470	2	0.5	4.5 (1.1–18.0)	81.0	18.1	63 (–49 to 175)
10–19	563	4 201	6	1.2	4.8 (2.2–10.8)	142.8	29.6	113 (–1 to 227)
≥20	441	5 034	6	2.2	2.8 (1.2–6.2)	119.2	43.2	76 (–19 to 171)

RR: standardised hospitalisation rate ratio; AER: absolute excess risk; CI: confidence interval; ALL: acute lymphoblastic leukaemia; CNS: central nervous system.
[a]Survivors only.
[b]Per 100,000 person-years.

TABLE 3. Cancer treatment characteristics of 28 Danish survivors with hyperthyroidism.

	Haematological cancers[a] (*n*)	CNS tumours (*n*)	Solid tumours[b] (*n*)	Total *n* (%)
Total	5	6	17	28 (100)
Surgery				
Yes	2	6	17	25 (89)
Partial thyroidectomy	–	–	1	1 (4)
Thyroidectomy	–	–	5	5 (18)
Other	2	6	11	19 (68)
No	3	–	–	3 (11)
Radiation				
Yes[c]	4	2	7	13 (46)
Total body irradiation	1	–	–	1 (4)
Head and neck	3	2	5	10 (36)
Chest	3	–	2	5 (18)
Other	–	–	3	3 (11)
No	1	4	10	15 (54)
Chemotherapy				
Yes	5	–	3	8 (29)
No	–	6	14	20 (71)
Bone marrow transplantation				
Yes	1	–	–	1 (4)
No	4	6	17	27 (96)

CNS: central nervous system.
[a]In the group of haematological cancers, we included leukaemia ($n = 1$), Hodgkin ($n = 3$) and non-Hodgkin lymphoma ($n = 1$).
[b]In the group of solid tumours we included thyroid cancers ($n = 6$), malignant bone tumours ($n = 3$), soft tissue sarcomas ($n = 2$), neuroblastomas ($n = 1$), malignant melanomas ($n = 1$), retinoblastomas ($n = 1$) and gonadal germ-cell tumours ($n = 2$).
[c]As some individuals received radiation in multiple areas, the total adds up to more than 13.

virtually no loss to follow-up and unbiased identification of population comparisons. However, cancer treatment data was only available for Danish survivors. Furthermore, complete medical records were available for only 28 of the 43, mainly because the records of many patients with childhood cancer diagnosed before 1970 had been destroyed or lost. As information on patients followed as outpatients were limited to Denmark and Sweden in the period after 1995, not all cases of hyperthyroidism were captured. As such underregistration also applies to the comparison cohort, however, this is not expected to affect the estimated relative risks. We only had Danish data on surgical procedures and prescriptions available from 1996. Thus, 4 out of 34 patients with a hyperthyroidism diagnosis in the hospital register that did not have prescriptions with any thyroid or anti-thyroid hormones possibly had thyroidectomy before 1996 and therefore no need for thyroid medications.

This study demonstrates that treatment of childhood cancer may result in the development of hyperthyroidism later in life. This may be contra intuitive, as cancer treatment

often leads to underactivity of the endocrine system and especially the thyroid gland. Even though hyperthyroidism is rare, it can influence the quality of life of a survivor and cause non-endocrine morbidity if not treated appropriately [24]. Therefore, it is important that clinicians responsible for long-term follow-up care of survivors are aware that hyperthyroidism may be a late effect following treatment for childhood cancer.

Acknowledgments

We would like to thank the ALiCCS board for their support in forming the ALiCCS cohort.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This study was supported by the Bjarne Saxhof Foundation.

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