Hospital contacts for endocrine disorders in Adult Life after Childhood Cancer in Scandinavia (ALiCCS): a population-based cohort study

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Summary

Background The pattern of endocrine disorders in long-term survivors of childhood cancer has not been investigated comprehensively. Here, we aimed to assess the lifetime risk of these disorders in Nordic survivors of childhood cancer.

Methods From the national cancer registries of Denmark, Finland, Iceland, Norway, and Sweden, we identified 31 723 1-year survivors of childhood cancer, notified since the start of registration in the 1940s and 1950s. From the national population registries, we randomly selected a comparison cohort of people matched by age, sex, and country. Study participants were linked to the national hospital registries, and observed numbers of first-time hospital contacts for endocrine disorders in survivors of childhood cancer were compared with the expected numbers derived from the population comparison cohort. We calculated the absolute excess risks attributable to status as a childhood cancer survivor and standardised hospitalisation rate ratios (SHRRs).

Findings Of the childhood cancer survivors, 3292 had contact with a hospital for an endocrine disorder, yielding a SHRR of 4·8 (95% CI 4·6–5·0); the highest risks were in survivors of leukaemia (SHRR 7·3 [95% CI 6·7–7·9]), CNS tumours (6·6 [6·2–7·0]), and Hodgkin's lymphoma (6·2 [5·6–7·0]). The absolute excess risk for endocrine disorders was roughly 1000 per 100 000 person-years before 20 years of age, and 400 per 100 000 person-years during the remaining lifetime. For children with cancer diagnosed at 5–9 years of age, the cumulative risk for endocrine disorders was highest, and reached 43% at the age of 60 years. Diagnoses of pituitary hypofunction (SHRR 88·0), hypothyroidism (9·9), and testicular and ovarian dysfunction (42·5 and 4·7, respectively) together constituted 61% (655 of 1078) of all excess disease-induced and treatment-induced endocrine disorders in survivors of childhood cancer.

Interpretation A cumulative risk for endocrine disorders at 60 years of age of above 40% in survivors of childhood cancer emphasises the importance of minimisation of damaging treatment, intensification of secondary prevention, and targeting of survivor follow-up throughout life. Since most long-term childhood cancer survivors are not followed in a specialised late-effect clinic, they are a growing challenge for the primary care physician and medical specialists working outside the late-effect area.

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Introduction

The number of survivors of childhood cancer is increasing steadily, mainly as a result of remarkable improvements in cancer treatment in the past five decades.[1,2] 5-year survival after all types of childhood cancer diagnosed around the turn of the 21st century was close to 80% in the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden).[1] However, with these advances in treatment, a wide range of health complications, not yet fully described, is becoming apparent. In the North American Childhood Cancer Survivor Study (CCSS), which included about 14 000 5-year survivors, two-thirds of all childhood cancer survivors were estimated to experience at least one chronic late effect,[3] often in the endocrine system, because of dysfunction of the hypothalamic–pituitary axis or direct damage to endocrine glands.[4] Substantially increased risks of hypothyroidism, ovarian failure, precocious and delayed puberty in survivors were identified for selected cancer types in the CCSS.[5–10] Whether this dismal picture also applies to children with cancer treated according to European standards is still not known. To address this particular question, we compared our results from northern Europe with those obtained in the North American CCSS study, whenever possible. In this study, we also present risk estimates for endocrine complications diagnosed in the 50 years and older age group, which has not previously been possible to investigate in large cohort studies of childhood cancer.

We studied endocrine disorders resulting from cancer or its treatment through long-term follow-up of childhood cancer survivors in the five Nordic countries through national cancer registries dating back to the 1940s and

1950s, with accurate follow-up of cancer survivors in population registries and information about a wide range of diagnostic outcomes from national hospital registries. We used the registries to measure hospital contacts for endocrine disorders in each participant, which is defined as all hospital admissions and outpatient visits for such disorders.

Methods

Patient and comparison cohorts

For **ALiCCS** see www.aliccs.org

This study is part of the Nordic collaborative cohort study Adult Life after Childhood Cancer in Scandinavia (ALiCCS), in which late complications after treatment for childhood cancer are being investigated.

The basic childhood cancer cohort comprised 43 909 people who had been reported to the cancer registries of the Nordic countries with a cancer diagnosed before the age of 20 years between the start of the registries in the 1940s and 1950s, and Dec 31, 2008. To be included in the cohort, patients had to be alive on or after the date on which centralised registration of residents of each country was operational with all required variables (Iceland, 1955; Norway, 1960; Denmark and Sweden, 1968; and Finland, 1971). All Nordic cancer registries are nationwide, and a cancer diagnosis is reported from several sources, which ensures virtually 100% coverage.[11–13] From the registries, we obtained information about 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 divided further into Hodgkin's and non-Hodgkin lymphomas.[14] Since the start of centralised civil registration in the Nordic countries, all residents have been assigned a unique personal identification number, which allows accurate linkage of information across registries.

To measure rates of morbidity of the endocrine system in the background population, we randomly selected 219 131 individuals from the population registries of the five countries, referred to as population comparisons. For each patient who had childhood cancer, five comparisons were chosen, who were alive on the date of cancer diagnosis of the corresponding patient, and were of the same sex, age, and country (for Denmark and Iceland) or the same county or municipality of residence (for Finland, Norway, and Sweden), and without a cancer diagnosis between the ages of 0–19 years. Although we aimed for a selection ratio of 1:5, fewer than five comparisons were available for 317 patients. Information about vital status and migration during follow-up was obtained from the population registers for both patients and population comparisons.

Before linkage of study participants to the respective national hospital register (see below), we excluded those in whom more than one primary cancer was diagnosed in childhood because they could not be classified unambiguously (305 patients); those who had died or emigrated before the start of the national hospital register (Sweden, stepwise inclusion of counties in 1964–87 and nationwide since 1987; Denmark, 1977; Iceland, 1999; Norway, 2008; Finland, before Jan 1, 1982; 7251 patients and 5146 comparisons); and those who had died or emigrated during the first year after the date of cancer diagnosis or an equivalent time lag for the population comparisons (3193 patients and 1093 comparisons). These exclusions resulted in a cohort of 33 160 1-year survivors of childhood cancer and a cohort of 212 892 population comparisons.

In accordance with Nordic regulations, data for cohort members were received and analysed without personal identifiers and the study was approved by either the national bioethics committees, the data protection authorities, or the national institute for health and welfare in the respective countries (Denmark: 2010–41–4334, Finland: THL/183/5·05·00/2012, Iceland: VSN 10–041, Norway: 2011/884/REC, and Sweden: Ö 10–2010, 2011/19).

	Recruitment period	Population recruited (n)		Follow-up period for endocrine disorders†	Population included in study (n)	
		Cancer survivors*	Population comparisons		Cancer survivors‡	Population comparisons
Denmark	1943–2008	9859	49 160	1977–2010§	7154	47 294
Finland	1953–2008	9147	45 665	1983–2009	7067	45 330
Iceland	1955–2008	699	3495	1999–2008	396	3349
Norway	1953–2008	9127	45 443	2008–2010	5250	40 993
Sweden	1958–2008	15 077	75 368	1968–2009¶	11 856	74 295
All countries	NA	43 909	219 131	NA	31 723	211 261

NA=not applicable. *Survivors of childhood cancer diagnosed in recruitment period and alive at the start of national population registration. †Period for which outcome data were available from the hospital registries. ‡1-year survivors alive at start of follow-up period. §Until Oct 31, 2010. ¶From 1968 to 1987, dependent on county—the inclusion of counties in Sweden was stepwise from 1968 to 1987, and nationwide since 1987.

Table 1: **Study population and follow-up period for endocrine disorders, by country**

Hospital contacts for endocrine disorders

The nationwide hospital registers contain information about all non-psychiatric hospital admissions in the five countries.[15,16] Registration is mandatory and is recorded by the treating physician. Each hospital admission initiates a record, which includes the personal identification number of the patient, the dates of admission and discharge, a primary discharge diagnosis, and a varying number of supplementary diagnoses coded according to the International Classification of Diseases (ICD), 7th to 10th revisions (ICD-7 to ICD-10). Outpatient visits were included in Denmark since 1995 and in Sweden since 2001. No data for outpatient visits were available from the hospital registers of Iceland, Finland, and Norway.

We identified all hospital admissions and outpatient visits (referred to as hospital contacts) with a primary or supplementary discharge diagnosis of the relevant endocrine sections of the ICD (ICD-7 codes 250–277, ICD-8 codes 240–258, ICD-9 codes 240–259, and ICD-10 codes E01–E35 and E89) for both childhood cancer survivors and population comparisons. We did not

include metabolic syndrome in this study because it was only recently introduced into the ICD-10 as a diagnostic entity. Linkage to the hospital registers showed that 732 survivors and 1415 comparisons had had a hospital contact for an endocrine disorder before the date of diagnosis of childhood cancer (or the corresponding date for the comparison participants); consequently, we excluded these people from the study. Since patients with a benign or malignant tumour of the pituitary gland are at high risk of endocrine disturbances that occur independently of their treatment, we excluded participants in whom a tumour of the pituitary gland had been diagnosed before they were 20 years old (508 survivors and ten comparisons). Finally, we excluded those with a congenital chromosomal abnormality (ICD-10 codes Q90–Q99; 197 survivors and 206 comparisons) because these disorders were judged to potentially confound causal associations between cancer treatment and endocrine late effects. Of the 31723 1-year survivors included, 25459 (80%) were under continuous follow-up 5 years or longer after cancer diagnosis.

Statistical analysis

Follow-up for endocrine disorders in the hospital registers began 1 year after the date of diagnosis of childhood cancer (and the corresponding date for the equivalent comparisons) or at the start of the hospital registers, whichever occurred most recently. Follow-up ended on the date of death, the date of emigration, or the closing date of the study, whichever occurred first. Follow-up also ended if a second primary cancer was diagnosed in a survivor or a first primary cancer in a population comparison participant. Diagnostic categories of ICD-7, ICD-8, and ICD-9 were adapted to those of the ICD-10 as far as was possible. If study participants had more than one hospital contact for a particular endocrine disorder, only the first record was retained, since it was presumed to be the date of diagnosis. We did risk analyses for any endocrine disorder and for each of 22 diagnostic categories. We compared the recorded numbers of first hospital contacts for an endocrine disorder in childhood cancer survivors with expected numbers derived from the appropriate country, sex, age, and calendar period specific morbidity rates of the population comparison cohort. We did not adjust for variables such as overweight, treatment for depression, physical activity, or other aspects of survivors' lifestyle because we view these factors as mediators, rather than confounders, of the association between childhood cancer and endocrine disorders. Similarly, we did not take into account the variability in survival rates between survivors of different cancers in the overall, cancer-specific risk estimates of endocrine disorders because we judge this variability to be part of the natural course of childhood cancer.

We estimated the significance and 95% CIs for the standardised hospitalisation rate ratio (SHRR—the ratio of observed-to-expected numbers of hospital contacts for each defined disease entity) with Fieller's theorem and assumed that the observed number of first hospital contacts follow a Poisson distribution. We derived absolute excess risk—that is, the additional risk for a hospital contact for an endocrine disorder—as the difference between the observed and expected first hospitalisation rates for endocrine disorders in cancer survivors per 100000 person-years of follow-up, with corresponding 95% CIs. We used SAS version 9.2 for all analyses.

Role of the funding source

The sponsor of the study had no role in the study design, data collection, analysis, access to raw data, interpretation

	Person-years at risk*	First hospital contacts (n)		SHRR (95% CI)	Hospitalisation rate (per 100 000 person-years)		AER (95% CI)
		Observed	Expected		Observed	Expected	
Sex							
Both	418528	3292	693·7	4·8 (4·6–5·0)	786·6	165·8	621 (594–648)
Male†	218534	1550	260·0	6·0 (5·6–6·4)	709·3	119·0	590 (555–626)
Female‡	199995	1742	433·8	4·0 (3·8–4·3)	871·0	216·9	654 (613–696)
Age group (years)							
0–9	43243	469	43·0	10·9 (9·4–12·6)	1084·6	99·5	985 (886–1084)
10–19	102724	1187	111·2	10·7 (9·8–11·7)	1155·5	108·2	1047 (981–1113)
20–29	122995	664	145·8	4·6 (4·1–5·0)	539·9	118·5	421 (380–463)
30–39	79176	453	141·8	3·2 (2·9–3·6)	572·2	179·1	393 (340–447)
40–49	43678	260	110·0	2·4 (2·1–2·7)	595·3	252·0	343 (269–417)
50–59	20033	176	86·9	2·0 (1·7–2·4)	878·5	433·7	445 (311–579)
≥60	6680	83	55·0	1·5 (1·2–1·9)	1242·6	823·7	419 (138–700)

SHRR=standardised hospitalisation rate ratio. AER=absolute excess risk per 100000 person-years. *Survivors only. †16979 male participants. ‡14744 female participants.

Table 2: **Observed and expected numbers of first hospital contacts for endocrine disorder of any type by sex and age in 31723 1-year survivors of childhood cancer in the Nordic countries**

	ICD-10 code	First hospital contacts (n)		SHRR (95% CI)	AER (95% CI)	Distribution of AER, % (n/N)
		Observed*	Expected*			
Atrophic disorders						
Pituitary hypofunction	E23·0–E23·3 and E89·3	1141	13·0	88·0 (72·1–107·5)	270 (254–285)	25% (270/1078)
Hypothyroidism	E03·2–E03·9 and E89·0	878	88·5	9·9 (9·0–11·0)	189 (175–203)	18% (189/1078)
Hypoparathyroidism	E20 and E89·2	80	3·1	26·3 (16·7–41·2)	18 (14–23)	2% (18/1078)
Diabetes	E10–E14 and E89·1	485	308·9	1·6 (1·4–1·7)	42 (31–53)	4% (42/1078)
Adrenal hypofunction	E27·1–E27·4 and E89·6	69	5·3	12·9 (8·8–18·9)	15 (11–19)	1% (15/1078)
Glandular hyperfunction						
Pituitary hyperfunction	E22	113	13·9	8·1 (6·3–10·5)	24 (19–29)	2% (24/1078)
Hyperthyroidism	E05	122	79·2	1·5 (1·3–1·9)	10 (5–16)	1% (10/1078)
Hyperparathyroidism	E21·0–E21·3	52	13·1	4·0 (2·9–5·5)	9 (6–13)	1% (9/1078)
Non-toxic thyroid goitre	E01 and E04	272	78·6	3·5 (3·0–4·0)	46 (38–54)	4% (46/1078)
Adrenal hyperfunction	E24, E26, E27·0, and E27·5	66	5·5	12·1 (8·3–17·7)	14 (11–18)	1% (14/1078)
Other and unspecified disorders						
Of the pituitary gland	E23·6–E23·7	137	2·7	50·0 (32·0–78·3)	32 (27–38)	3% (32/1078)
Of the thyroid gland	E07	38	7·5	5·1 (3·4–7·6)	7 (4–10)	1% (7/1078)
Of the pancreas	E15 and E16	68	26·8	2·5 (1·9–3·3)	10 (6–14)	1% (10/1078)
Of the adrenal glands	E27·8–E27·9	15	1·5	9·8 (4·6–20·8)	3 (1–5)	<1% (3/1078)
Inflammatory disorders						
Thyroiditis	E06	59	26·4	2·2 (1·7–3·0)	8 (4–11)	1% (8/1078)
Sex hormone dysfunction						
Ovarian dysfunction	E28 and E89·4	266	57·1	4·7 (4·0–5·4)	104 (88–121)	10% (104/1078)
Testicular dysfunction	E29 and E89·5	206	4·9	42·5 (30·4–59·4)	92 (79–105)	9% (92/1078)
Precocious puberty	E30·1	112	7·5	16·1 (11·9–21·9)	27 (22–32)	3% (27/1078)
Delayed puberty	E30·0	109	13·0	8·4 (6·4–11·0)	23 (18–28)	2% (23/1078)
Other disorders of puberty	E30·8 and E30·9	33	2·3	14·5 (8·2–25·6)	7 (5–10)	1% (7/1078)
Restricted growth						
Restricted growth	E34·3	310	26·1	11·9 (10·0–14·2)	68 (60–76)	6% (68/1078)
Other endocrine disorders						
Other endocrine disorders†	E21·4–21·5, E31, E32, E34, E35, and E89·8–E89·9	292	39·1	7·5 (6·4–8·8)	60 (52–68)	6% (60/1078)

ICD-10=International Classification of Diseases, tenth revision. SHRR=standardised hospitalisation rate ratio. AER=absolute excess risk per 100 000 person-years. *The numbers of patients included in each of the 22 categories of endocrine disorders add up to more than the total number of patients with endocrine disorder because 33% (1095/3292) of survivors with endocrine disorders had several diagnoses and were categorised into more than one diagnostic category. †Includes postprocedural endocrine disorders.

Table 3: **Observed and expected numbers of first hospital contacts for endocrine disorders of any type or one or more of 22 subcategories of endocrine disorder in 31 723 1-year survivors of childhood cancer in the Nordic countries**

of the data, or in writing this report. The corresponding author had full access to all the data in the study and the final responsibility to submit for publication. Data manager Andrea Bautz also had access to the raw data.

Results

We included 31723 1-year survivors of childhood cancer and 211261 population comparisons in our analyses (table 1). We followed up survivors of childhood cancer in the national hospital registers for 418528 person-years (median 10 years, range 0–42 years), during which time 3292 1-year survivors had at least one hospital contact for an endocrine disorder; 693·7 patients would have been expected, which yielded an overall SHRR of 4·8 (table 2). The SHRRs for the individual countries were: Denmark 4·1 (95% CI 3·8–4·5), n=810; Finland 5·3 (4·7–5·9), n=500; Iceland 2·6 (0·9–7·8), n=4; Norway 4·2 (3·7–4·7), n=407; and Sweden 5·2 (4·9–5·5), n=1571. On the basis of observed and expected overall rates of hospital contacts for endocrine disorders of 786·6 and 165·8 per 100000 person-years, the absolute excess risk was 621 per 100000 person-years (table 2). Thus, for each additional year of follow-up, a new excess endocrine disorder was diagnosed at hospital for an average of six per 1000 survivors of childhood cancer. The noticeable difference in the sex-specific relative risk for an endocrine disorder (SHRR 6·0 in men *vs* 4·0 in women) is not due to more treatment-related complications in male than in female survivors (table 2) but rather an effect of a notable lower background rate of endocrine disorders in male than in female cancer survivors (table 2).

In each age group, the observed number of first hospital contacts for any type of endocrine disorder was

higher than was expected (table 2). Although the SHRR increased significantly at all ages, the degree of increase diminished substantially with increasing age of the survivor, from a SHRR of 10·9 and 10·7 in the first two decades of life to one of 1·5 in people aged 60 years or older. The absolute excess risk did not show similar variation; after about 1000 excess endocrine disorders per 100 000 person-years in the first two decades of life, the absolute excess risk stabilised at roughly 400 excess endocrine hospital contacts per 100 000 person-years throughout the remaining lifetime (table 2).

Childhood cancer survivors were at a significantly higher risk for a hospital contact for one or more of the 22 diagnostic categories than were population comparisons (table 3). The highest relative risks were for pituitary hypofunction (SHRR 88·0), other and unspecified disorders of the pituitary gland (50·0), testicular dysfunction (42·5), hypoparathyroidism (26·3), and precocious puberty (16·1). Table 3 also shows that pituitary hypofunction was the leading adverse outcome, with an absolute excess risk of 270 per 100 000 person-years, followed by hypothyroidism (189), ovarian dysfunction (104), and testicular dysfunction (92). These four outcomes together constituted 61% (655/1078) of all disease-induced and treatment-induced endocrine disorders recorded in the survivor cohort (table 3). Of survivors with endocrine problems, 67% (2197/3292) had a hospital contact for disorders in one diagnostic category, and 33% (1095/3292) had a hospital contact for disorders in two or more diagnostic categories.

Figure 1 shows the observed and expected age-specific rates of a first hospital contact for any type of endocrine disorder and for a set of well-defined diagnostic categories. Although hypothyroidism was a treatment complication in all age groups, pituitary hypofunction and ovarian dysfunction were mainly reported before 40 years of age.

We stratified the survivor cohort into those whose cancers were diagnosed when they were aged 0–4, 5–9, 10–14, and 15–19 years and calculated the cumulative risks for an endocrine disorder of any type by age (figure 2). Survivors whose cancer was diagnosed when they were 5–9 years old had the highest cumulative risk, with 35% of survivors being affected at the age of 40 years and 43% at 60 years, especially because many survivors were diagnosed with pituitary hypofunction.

For most survivors whose cancer was diagnosed in the most recent decades, we were able to establish a hospitalisation history covering the survivor's subsequent life. For survivors with cancer diagnosed in 1975–89, the cumulative risk for endocrine disorders was 42% at the age of 60 years, and for those diagnosed in 1990–2008 the cumulative risk was 38% at the age of 40 years. The high risk for endocrine disorders in the latter subcohort was partly explained by especially high risks for pituitary dysfunction (mainly hypofunction, but also survivors with hyperfunction), hypothyroidism, and gonadal dysfunction (data not shown).

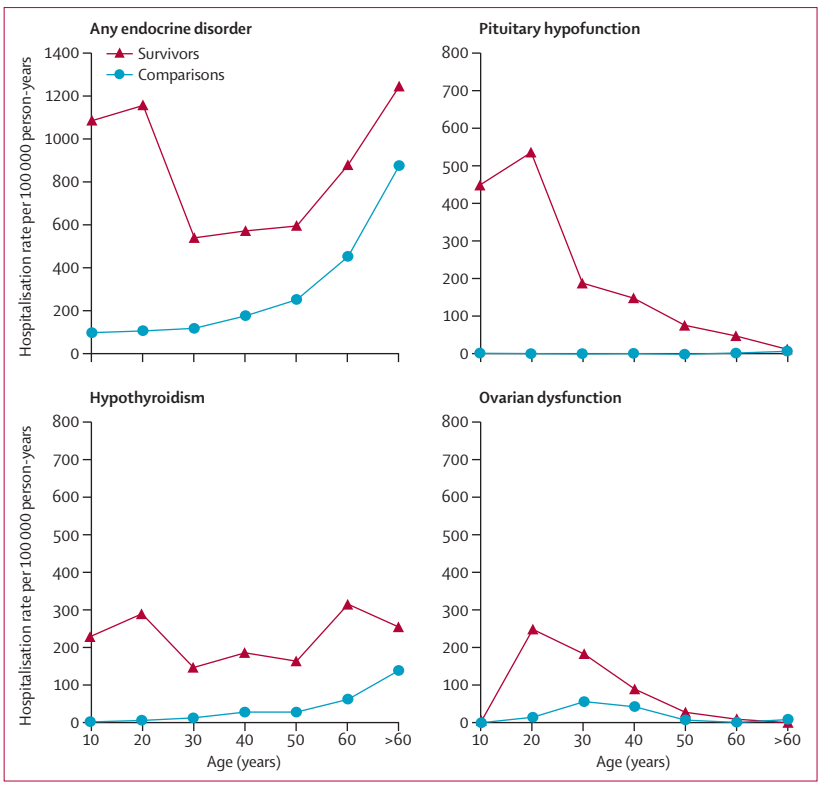

Figure 1: **Observed and expected hospitalisation rates per 100 000 person-years for any and selected endocrine disorders in 31 723 1-year survivors of childhood cancer in the Nordic countries by age at first hospital contact for an endocrine disorder**

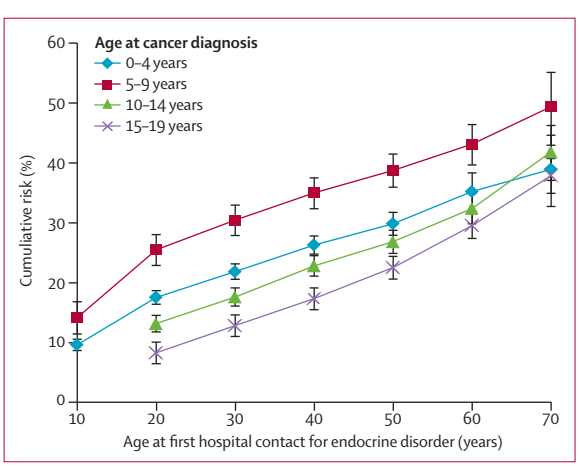

Figure 2: **Cumulative risk for a first hospital contact for any type of endocrine disorder by age at first hospital contact for an endocrine disorder and by age at cancer diagnosis**
Error bars are 95% CIs.

Survivors of all the main types of childhood cancers had a significantly increased absolute excess risk for a subsequent hospital contact for a diagnosis of the endocrine system, especially survivors of leukaemia, Hodgkin's lymphoma, and CNS tumours (figure 3). Additionally, table 4 shows the relative risks for a selected set of combinations of childhood cancer and endocrine

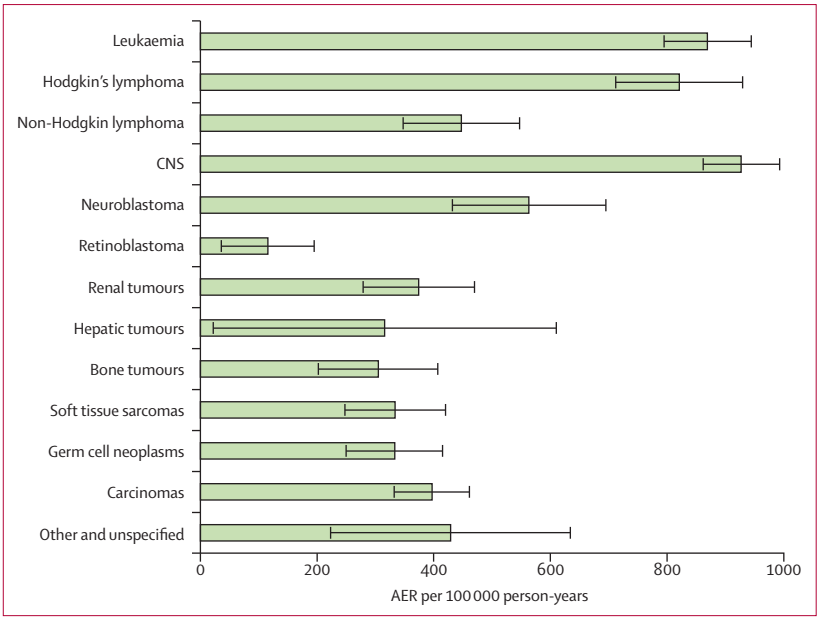

Figure 3: **Absolute excess risk per 100 000 person-years for a first hospital contact for any endocrine disorder by main childhood cancer diagnosis (International Classification of Childhood Cancer)**
AER=absolute excess risk. Error bars are 95% CIs.

	First hospital contacts in survivors (n)	SHRR (95% CI)
Leukaemia (n=6835)		
Any endocrine disorder	711	7·3 (6·7–7·9)
Testicular dysfunction	120	152·7 (106·0–220·0)
Pituitary hypofunction	276	106·6 (86·3–131·7)
Other pituitary disorders	31	86·2 (47·9–155·0)
Other disorders of puberty	18	22·8 (13·0–40·0)
Hodgkin's lymphoma (n=2425)		
Any endocrine disorder	317	6·2 (5·6–7·0)
Hypothyroidism	185	27·7 (23·6–32·6)
Non-Hodgkin lymphoma (n=1756)		
Any endocrine disorder	140	4·0 (3·4–4·7)
Pituitary hypofunction	28	38·5 (25·4–58·4)
Other pituitary disorders	4	31·2 (10·6–91·8)
Testicular dysfunction	11	29·2 (15·3–55·7)
CNS tumours (n=7274)		
Any endocrine disorder	1071	6·6 (6·2–7·0)
Pituitary hypofunction	655	215·2 (175·2–264·3)
Other pituitary disorders	85	130·3 (81·9–207·1)
Precocious puberty	88	58·3 (41·4–82·1)
Restricted growth	143	25·5 (20·5–31·6)
Adrenal hypofunction	29	22·3 (14·0–35·6)
Pituitary hyperfunction	67	21·4 (15·8–29·0)
Adrenal hyperfunction	24	19·8 (12·0–32·7)
Hypothyroidism	235	11·6 (10·0–13·5)
Neuroblastoma (n=1318)		
Any endocrine disorder	110	5·0 (4·1–6·0)
Pituitary hypofunction	30	53·6 (36·0–80·0)
Testicular dysfunction	6	40·4 (16·9–96·5)
Retinoblastoma (n=822)		
Any endocrine disorder	41	1·8 (1·3–2·5)
Pituitary hypofunction	10	23·7 (12·4–45·6)

(Table 4 continues on next page)

disorders for which the lower 95% confidence limit of SHRR was 10 or higher. Survivors of CNS tumours had exceptionally high risks for pituitary hypofunction, other pituitary disorders, and precocious puberty (table 4). Survivors of childhood leukaemia had highly increased risks for pituitary hypofunction and other pituitary disorders, although the highest risk in this group was for testicular dysfunction (table 4).

Discussion

This population-based follow-up study of more than 30 000 1-year survivors of childhood cancer in five Nordic countries showed that this group had an overall 4·8-times increase in risk for a hospital contact for any endocrine disorder covered in the endocrine chapter of ICD-10. The risk was highest for survivors of leukaemia and CNS tumours. The relative increase decreased by age, from an SHRR of 10 or higher in the two first decades of life to 1·5 for survivors aged 60 years or older. This reduction was partly a consequence of an age-dependent increase in the background rates of endocrine disorders and partly an effect of extraordinarily high absolute excess risks for endocrine disorders during the first two decades of life, mainly explained by high numbers of early-onset pituitary hypofunction in survivors treated for CNS tumours (age 0–9 years, absolute excess risk 1559 per 100 000 person-years; age 10–19 years, absolute excess risk 1200 per 100 000 person-years), who were probably given cranial radiation. The absolute excess risk of survivors was quite uniform throughout adulthood and middle age, equivalent to roughly four new excess endocrine disorders per 1000 survivors per year of follow-up. An especially high cumulative risk for an endocrine disorder in survivors whose cancers were diagnosed when they were 5–9 years of age (43% at the age of 60 years) was at least partly explained by an extraordinarily high number of pituitary dysfunctions, which in turn is caused by the high proportions of CNS tumours (1777 of 5586) and leukaemia (1687 of 5586) in this age group. Of the 22 diagnostic categories investigated, pituitary hypofunction predominated, with 1141 survivors affected (SHRR 88), and represented 25% (270 of 1078) of all endocrine disorders. Other common endocrine outcomes in survivors were hypothyroidism and dysfunction of the gonads, each comprising almost 20% of the endocrine late effect pattern (189 with hypothyroidism and 196 with dysfunction of gonads out of 1078 excess hospital contacts) (panel).

Despite fundamental differences in methods between our study (in which we used outcome data derived from hospital discharge records and included a large population-based comparison cohort) and the CCSS (in which

	First hospital contacts in survivors (n)	SHRR (95% CI)
(Continued from previous page)		
Renal tumours (n=1409)		
Any endocrine disorder	112	3·7 (3·1–4·5)
Hepatic tumours (n=241)		
Any endocrine disorder	9	3·1 (1·6–5·9)
Malignant bone tumours (n=1533)		
Any endocrine disorder	88	2·7 (2·2–3·3)
Testicular dysfunction	8	31·1 (14·7–65·7)
Soft tissue sarcomas (n=1995)		
Any endocrine disorder	143	2·8 (2·4–3·3)
Pituitary hypofunction	50	60·4 (43·1–84·6)
Testicular dysfunction	10	29·7 (14·9–59·2)
Germ cell neoplasms (n=2125)		
Any endocrine disorder	142	2·9 (2·4–3·4)
Pituitary hypofunction	32	36·5 (24·6–54·2)
Testicular dysfunction	26	59·0 (36·9–94·4)
Carcinomas and other malignant epithelial neoplasms (n=3691)		
Any endocrine disorder	356	2·9 (2·6–3·2)
Hypoparathyroidism	55	86·3 (57·0–130·6)
Other and unspecified neoplasms (n=472)		
Any endocrine disorder	34	3·2 (2·3–4·5)
Pituitary hypofunction	13	73·6 (41·4–130·8)

ICCC=International Classification of Childhood Cancer. SHRR=standardised hospitalisation rate ratio.

Table 4: **Standardised hospitalisation rate ratios for endocrine disorders of any type and for subcategories of endocrine disorders distinguished by a lower 95% confidence limit of ≥10 by main diagnostic group of childhood cancer (ICCC)**

	ALiCCS	CCSS	
	SHRR (95% CI) or cumulative risk (%)	RR (95% CI) or cumulative risk (%)	Study
Hypothyroidism			
Hodgkin's lymphoma	SHRR 27·7 (23·6–32·6)	RR 17·1 (12·5–24·2)	Sklar et al (2000)[6]
CNS cancer	SHRR 11·6 (10·0–13·5)	RR 14·3 (9·7–21·0)	Gurney et al (2003)[7]
Soft tissue sarcoma or rhabdomyosarcoma	Soft tissue sarcoma: SHRR 4·7 (3·3–6·9)	Rhabdomyosarcoma: RR 6·9 (4·1–11·3)	Punyko et al (2005)[8]
Ovarian dysfunction*			
All cancers†	Cumulative risk 5·5%	Cumulative risk 6·3%	Green et al (2009)[9]
Precocious puberty			
Leukaemia or acute lymphoblastic leukaemia	Leukaemia: SHRR 6·9 (4·3–11·2)	Acute lymphoblastic leukaemia: RR 5·0–11·2‡	Chow et al (2008)[5]
CNS cancer	SHRR 58·3 (41·5–82·1)	RR 14·1 (7·0–30·9)	Armstrong et al (2009)[10]
Delayed puberty			
Leukaemia or ALL	Leukaemia: SHRR 12·6 (9·2–17·3)	Acute lymphoblastic leukaemia: RR 2·2–4·8‡	Chow et al (2008)[5]
CNS cancers	SHRR 7·1 (4·5–11·2)	RR 6·6 (3·4–11·4)	Armstrong et al (2009)[10]

ALiCCS= Adult Life after Childhood Cancer in Scandinavia. CCSS= Childhood Cancer Survivor Study. SHRR=standardised hospitalisation rate ratio. RR=relative risk. ALL=acute lymphoblastic leukaemia. *CCSS use ovarian failure as outcome; we used ovarian dysfunction (ICD-10 codes E28 and E89·4). †CCSS includes leukaemia, lymphoma, neuroblastoma, CNS tumour, bone tumour, kidney tumour, and soft tissue sarcoma. ‡Depends on dose and location of radiotherapy.

Table 5: **Similarity of risk estimates obtained in the ALiCCS study and the CCSS for comparable combinations of childhood cancer and endocrine disorders**

investigators used self-reported outcome data and did comparisons with a sibling cohort),[23] the results were similar in virtually all situations in which the two studies can be meaningfully compared (table 5). The most notable differences in results between our study and the CCSS were the relative risks for hypothyroidism in survivors of Hodgkin's lymphoma (27·7 in our study *vs* 17·1 in CCSS),[6] precocious puberty in survivors of CNS tumours (58·3 *vs* 14·1),[10] and for delayed puberty in survivors of leukaemia (12·6 *vs* 2·2–4·8, depending on dose and location of radiotherapy).[5] The differences could be at least partly explained by surveillance bias caused by use of hospital-based diagnostic information in the Nordic study. In the British Childhood Cancer Survivor Study comprising of more than 17 000 5-year survivors of cancer, the frequency of hypothyroidism has been estimated to be 7·7%, compared with a cumulative risk of 12·5% at age 60 years in our study.[25]

To obtain the most appropriate date of diagnosis for endocrine outcomes, we began follow-up of childhood cancer survivors 1 year after the date of cancer diagnosis. However, endocrine outcomes that occurred 1–4 years after cancer diagnosis might to some extent have been attributable to side-effects of prolonged treatment for cancer or relapse, and this difference should be taken into account in comparisons of our results with those of the CCSS. Moreover, we used hospital-based diagnoses made by physicians as markers of disease outcome. Although this approach increased the validity of the diagnostic information, late effects such as hypothyroidism and hypogonadism, which do not always lead to a hospital admission, might have been missed. Many patients with less severe and easily compensational endocrine disorders are seen only by their general practitioner, or are followed in an outpatient setting. Thus, for the Danish and Swedish datasets, in which outpatient information was available for part of the study period, we noted that 47% (1117 of 2381) of patients with endocrine disorders were followed exclusively in an outpatient setting (they were never admitted to hospital for their disease); this finding indicates that many endocrine outcomes were missed for most of our study material that had no information about outpatient activities. However, since this limitation also applies to the comparison cohort, the validity of the relative risk estimates is acceptable, although it is restricted to complications that need hospital contact. Thus, in a separate analysis of the Danish and Swedish survivors, we reported a SHRR of 4·6 (95% CI 4·3–5·0) for admission to hospital with endocrine disorders, and one of 4·8 (4·5–5·0) for admission to hospital or outpatient visits with endocrine disorders, which indicates a tendency for slightly higher risk estimates when outpatient information was included. This subanalysis suggests that Nordic data underestimate, rather than overestimate, the risk for endocrine late effects after treatment for childhood cancer.

Overall, 36% (1571 of 4399) of endocrine disorders in survivors and 20% (1156 of 5647) in comparison participants were registered exclusively as a supplementary diagnosis. Since supplementary diagnoses do not generally represent the main reason for a hospital admission, we tested the robustness of the risk estimates from the main analysis in a restricted analysis in which we used only information about endocrine disorders that were captured through a primary diagnosis during follow-up. In this analysis, most risk estimates were only slightly lower than were those obtained in the main analysis, with an overall estimate for endocrine disorders decreasing from 4·8 (95% CI 4·6–5·1) to 4·4 (4·2–4·6), which suggests a high degree of stability.

The main aim of this report of late effects in childhood cancer survivors was to give a complete overview of the risk for each of all types of endocrine disorders included in the ICD-10—that is, to give an exhaustive endocrine risk profile of childhood cancer survivors. A large amount of the endocrine late effects is likely to be ascribed to cranial and local radiation treatment and, for gonadal damage, also chemotherapy. However, in our analysis we were not able to quantify the risks associated with radiation treatment and chemotherapy. The usefulness of the Nordic cancer registers in research of late effects in childhood cancer survivors is limited by insufficient or completely absent information about treatment. The existing information is too crude to allow for meaningful analyses linking type and dose of chemotherapy and radiation with specific endocrine disorders. To compensate for this problem, case-control studies nested in the childhood cancer survivor cohort or case-cohort studies with collection of treatment data from the medical records of cancer survivors need to be organised. Such studies, designed to quantify the damaging effects of the various components of the childhood cancer treatment in regard to a selected set of high-risk endocrine outcomes, are ongoing with the Nordic childhood cancer survivor cohort.

The prospective nature of our study, with registration of malignant disease in advance and independently of registration of endocrine outcomes, close-to-complete cancer registration, and virtually no loss to follow-up, reduces the likelihood that biases caused by selection of study participants or differential reporting of endocrine outcomes were introduced. Additionally, we included all childhood cancer patients in the five Nordic countries, and all types of cancer. Further strengths include the unbiased identification of population comparison participants (instead of siblings) and unusually long follow-up of study participants, even to the oldest ages, including those older than 60 years. Since the study is based on more than 30 000 1-year survivors, of whom more than 25 000 were 5-year survivors, the statistical power of the study is unparalleled and the risk estimates correspondingly accurate. Finally, this cohort study describes the endocrine late-effect pattern resulting from childhood cancer treatments as practised in northern Europe over time and by the exclusive use of medically verified diagnostic information (instead of self-reported disease). The validity of the study is corroborated by the notable similarities in overall risk estimates for endocrine disorders reported between the five participating countries. Nevertheless, we cannot exclude the possibility that our results were affected by better medical surveillance of the survivors than of the population comparisons. Surveillance bias would preferentially affect less well defined medical problems, such as disorders of puberty or dysfunction of the gonads.

For study participants diagnosed with cancer several years before the start of the hospital registers, an unknown proportion of hospital contacts could have occurred because of prevalent endocrine disorders rather than incident events. This limitation of data availability suggests that endocrine disorders detected before the start of the

Panel: Research in context

Systematic review

We searched PubMed, with no date or language restrictions, with the search terms "childhood cancer", "endocrine disorders", "late effects", "hypothyroidism", "pituitary hypofunction", "diabetes", "puberty timing", "ovarian dysfunction", and "testicular dysfunction". Our search showed that endocrine organ dysfunctions in survivors of childhood cancer have been recognised as late sequelae since the 1970s.[17] During the next few decades, many clinical studies showed links between radiation therapy, especially cranial and total body irradiation, and a wide range of subsequent endocrine disturbances, and associations between exposure to alkylating agents and the development of hypogonadism and infertility.[18–22] In general, these studies were based on small, uncontrolled series of survivors, which obviated the computation of relative and/or absolute risk; the studies were limited further by short or incomplete follow-up. More recently, selected types of endocrine organ dysfunction were investigated in the CCSS, which involved about 14 000 5-year survivors and 4000 sibling controls.[23] The CCSS included detailed information about treatment regimens, but outcomes were self-reported, the cohort was limited to patients diagnosed with cancer in 1970–86, and 31% of survivors (6222 of 20 276 eligible survivors) were lost to follow-up or did not respond to the baseline questionnaire.[24] We therefore decided to use hospital diagnoses for Nordic childhood cancer survivors and population comparisons to determine the survivors' relative and absolute risks of a broad range of endocrine late effects throughout life, with minimum loss to follow-up.

Interpretation

Long-term follow-up of 1-year childhood cancer survivors exposed to Nordic treatment regimens since the 1940s and 1950s showed a notably increased risk for hospital contacts for a wide range of endocrine disorders. The risk estimates for outcomes associated with specific childhood cancers were largely comparable to those reported from the USA. In our study, pituitary hypofunction, hypothyroidism, and gonadal dysfunction were the most prevalent disease-induced and treatment-induced late effects. The risk was especially high for survivors of leukaemia and CNS tumours and for those whose cancer was diagnosed when they were 5–9 years of age. Our study was based on medically verified diagnoses and survivors were followed up well beyond 40 years of age. Our findings add to the growing body of evidence that endocrine late effects remain a main health concern of survivors of childhood cancer throughout life. With the progressively increasing survival rates of childhood cancer, this fact emphasises the importance of minimisation of damaging treatment, intensification of secondary prevention, and following of survivors for life.

hospital registers might remain unnoticed until later hospital contact, and thus be shifted towards an older age group, which potentially affects the validity of the age-specific risk estimates. Additionally, the delayed inclusion of study participants might have caused some selection bias, favouring representation from cancers with better survival rates and patients with better outcomes. However, a sensitivity analysis with exclusion of participants with cancer diagnosed more than 10 years before the start of the hospital registers did not change the age-specific risk estimates to any appreciable extent.

Survivors of childhood cancer have previously been shown to be at increased risk for several diseases, such as new primary cancers, cardiovascular and pulmonary disorders, and reproductive difficulties. The increased risk for endocrine disorders reported in this study is likely to add substantially to the burden of late complications in survivors. Since most long-term childhood cancer survivors are not followed at late-effect clinics in a highly specialised medical environment, this population constitutes a specific and increasing challenge for primary care physicians and for medical specialists working outside the late-effect area.

Contributors

SdFL is the principal investigator. She has contributed substantially to the study design, literature search, collection and assembly of data, data analyses, and interpretation. She has written all drafts and the final version of the report and created all the tables and figures. JHO, JFW, and HH contributed to the conception and design. TG and HA contributed to the study design. JHO, TG, LT, HA, NM, and FW contributed to the collection and assembly of data. JHO, JFW, TG, ASH, TGB, PHA, KH, and HH contributed to the data analyses and interpretation. All authors contributed to preparation of the report and approved the final version.

Declaration of interests

SdFL has a minor stock ownership in Novo Nordisk. The other authors declare that they have no competing interests.

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References

1 Gatta G, Zigon G, Capocaccia R, et al, and the EUROCARE Working Group. Survival of European children and young adults with cancer diagnosed 1995–2002. *Eur J Cancer* 2009; **45:** 992–1005.

2 de Nully Brown P, Olsen JH, Hertz H, Carstensen B, Bautz A. Trends in survival after childhood cancer in Denmark, 1943–87: a population-based study. *Acta Paediatr* 1995; **84:** 316–24.

3 Oeffinger KC, Mertens AC, Sklar CA, et al, and the Childhood Cancer Survivor Study. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med* 2006; **355:** 1572–82.

4 Meacham L. Endocrine late effects of childhood cancer therapy. *Curr Probl Pediatr Adolesc Health Care* 2003; **33:** 217–42.

5 Chow EJ, Friedman DL, Yasui Y, et al. Timing of menarche among survivors of childhood acute lymphoblastic leukemia: a report from the Childhood Cancer Survivor Study. *Pediatr Blood Cancer* 2008; **50:** 854–58.

6 Sklar C, Whitton J, Mertens A, et al. Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the Childhood Cancer Survivor Study. *J Clin Endocrinol Metab* 2000; **85:** 3227–32.

7 Gurney JG, Kadan-Lottick NS, Packer RJ, et al, and the Childhood Cancer Survivor Study. Endocrine and cardiovascular late effects among adult survivors of childhood brain tumors: Childhood Cancer Survivor Study. *Cancer* 2003; **97:** 663–73.

8 Punyko JA, Mertens AC, Gurney JG, et al. Long-term medical effects of childhood and adolescent rhabdomyosarcoma: a report from the childhood cancer survivor study. *Pediatr Blood Cancer* 2005; **44:** 643–53.

9 Green DM, Sklar CA, Boice JD Jr, et al. Ovarian failure and reproductive outcomes after childhood cancer treatment: results from the Childhood Cancer Survivor Study. *J Clin Oncol* 2009; **27:** 2374–81.

10 Armstrong GT, Whitton JA, Gajjar A, et al. Abnormal timing of menarche in survivors of central nervous system tumors: a report from the Childhood Cancer Survivor Study. *Cancer* 2009; **115:** 2562–70.

11 Tulinius H, Storm HH, Pukkala E, Andersen A, Ericsson J. Cancer in the Nordic countries, 1981–86. A joint publication of the five Nordic Cancer Registries. *APMIS Suppl* 1992; **31:** 1–194.

12 Gjerstorff ML. The Danish Cancer Registry. *Scand J Public Health* 2011; **39** (suppl)**:** 42–45.

13 Sigurdardottir LG, Jonasson JG, Stefansdottir S, et al. Data quality at the Icelandic Cancer Registry: comparability, validity, timeliness and completeness. *Acta Oncol* 2012; **51:** 880–89.

14 Birch JM, Marsden HB. A classification scheme for childhood cancer. *Int J Cancer* 1987; **40:** 620–24.

15 Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011; **11:** 450.

16 Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011; **39** (suppl)**:** 30–33.

17 Nandagopal R, Laverdière C, Mulrooney D, Hudson MM, Meacham L. Endocrine late effects of childhood cancer therapy: a report from the Children's Oncology Group. *Horm Res* 2008; **69:** 65–74.

18 Constine LS, Woolf PD, Cann D, et al. Hypothalamic-pituitary dysfunction after radiation for brain tumors. *N Engl J Med* 1993; **328:** 87–94.

19 Shalet SM, Beardwell CG, Morris-Jones P, Bamford FN, Ribeiro GG, Pearson D. Growth hormone deficiency in children with brain tumors. *Cancer* 1976; **37** (suppl)**:** 1144–48.

20 Teinturier C, Hartmann O, Valteau-Couanet D, Benhamou E, Bougneres PF. Ovarian function after autologous bone marrow transplantation in childhood: high-dose busulfan is a major cause of ovarian failure. *Bone Marrow Transplant* 1998; **22:** 989–94.

21 Oberfield SE, Soranno D, Nirenberg A, et al. Age at onset of puberty following high-dose central nervous system radiation therapy. *Arch Pediatr Adolesc Med* 1996; **150:** 589–92.

22 Horning SJ, Hoppe RT, Kaplan HS, Rosenberg SA. Female reproductive potential after treatment for Hodgkin's disease. *N Engl J Med* 1981; **304:** 1377–82.

23 Robison LL, Armstrong GT, Boice JD, et al. The Childhood Cancer Survivor Study: a National Cancer Institute-supported resource for outcome and intervention research. *J Clin Oncol* 2009; **27:** 2308–18.

24 Robison LL, Mertens AC, Boice JD, et al. Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. *Med Pediatr Oncol* 2002; **38:** 229–39.

25 Brabant G, Toogood AA, Shalet SM, et al. Hypothyroidism following childhood cancer therapy-an under diagnosed complication. *Int J Cancer* 2012; **130:** 1145–50.