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ORIGINAL ARTICLE

Incidence and time trends of childhood cancer in Denmark, 1943–2014

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ABSTRACT

Background: Surveillance of childhood cancer incidence is informative for etiologic research and health policy. However, high-quality data covering several decades of virtually complete cancer diagnosis in children is sparse.

Methods: Incident cases of childhood cancer (0–19 years at diagnosis), classified according to Birch and Marsden's International Classification of Childhood Cancer, first edition (ICCC-1), were identified in the Danish Cancer Registry and used to calculate age-standardized incidence rates (ASRs) and estimated annual percentage change (EAPC) separately for 1943–1977 (early period) and 1977–2014 (recent period).

Results: During 1943–2014, 15,184 childhood cancer cases were reported. The ASR for any cancer was 13.0 per 100 000 person-years in the early period (EAPC 0.55%; 95% CI 0.30–0.80) and 17.7 per 100 000 person-years in the recent period (EAPC 1.16%; 95% CI 0.96–1.36). In both periods, the increasing trend was seen in both boys (EAPC 0.69%; 95% CI 0.43–0.96/EAPC 0.96%; 95% CI 0.75–1.17) and girls (EAPC 0.37%; 95% CI −0.01–0.75/EAPC 1.41%; 95% CI 1.11–1.72) and in children aged 0–14 years (EAPC 0.53%; 95% CI 0.26–0.80/EAPC 0.86%; 95% CI 0.64–1.08) and 15–19 years (EAPC 0.60%; 95% CI 0.19–1.02/EAPC 1.97%; 95% CI 1.67–2.28). Increasing trends were observed for all main diagnostic groups.

Conclusions: The incidence of childhood cancer in Denmark has increased since the 1940s, especially since 1977 and in older children. In recent years the increase has been most pronounced among girls.

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Introduction

Childhood cancer is a severe, potentially lethal condition and is the leading cause of disease-related death among children in high-income countries [1]. Its etiology is, however, virtually unknown. Describing incidence patterns may provide useful indications of etiologic associations. Differences in geographic incidence have been used to support hypotheses of associations with exposures related to modern lifestyles, particularly leukemia [2,3]. Denmark previously had one of the highest incidence rates of childhood cancer in the world [4]; however, this conclusion was based on older studies [5–7]. Two studies reported a slight increase in the incidence of childhood cancer in boys, but not in girls in Denmark between 1943 and the 1980s [5,6]. The most recent study, which included data up to 1999, showed an overall increasing trend [7]. A number of studies outside Denmark have reported modest increases in childhood cancer incidence rates since the 1970s [8–10]. In Europe during 1970–1999, the incidence increased by 1.0% per year for children aged 0–14 years and by 1.5% per year for those aged 15–19 years [10]. Data from the recently published third volume of the International Incidence of Childhood Cancer show increases in overall global childhood cancer rates between the 1980s and the 2000s [11]. If the increase is true and not an artifact due to incomplete or invalid data or improved diagnostics and reporting, it could indicate changes in environmental risk factors [12], which is important for understanding and preventing childhood cancer. Several of the studies cited above are based on potentially insufficient data due to inconsistent and/or incomplete reporting over time [13]. In contrast, Denmark has one of the oldest, most comprehensive cancer registries in the world. The data on incident cancers are of high quality, and the completeness of the Registry is estimated to be 95–98% [14,15]. Thus, Danish Registry data offer an ideal setting for studying the incidence and time trends of childhood cancer. The objective of this study was to determine the incidence of and time trends in childhood cancer in Denmark, which have not been examined for more than 15 years.

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Supplemental data for this article can be accessed here.

Material and methods

The Danish Cancer Registry and case definition

We identified all incident cases of primary childhood cancer (including benign brain tumors) diagnosed in Danish residents aged 0–19 years, during the period January 1, 1943 to December 31, 2014, in the Danish Cancer Registry, a nationwide register of all cancers diagnosed in Denmark since 1943, with mandatory reporting since 1987 [15–17]. The Registry receives notifications from all hospital departments, general practitioners, and practicing specialists as well as autopsy reports from institutes of pathology and forensic medicine. The information is supplemented annually with death certificates from the Danish Register of Causes of Death and, since 1987, by linkage to the Danish National Patient Register. In 2004, the Cancer Registry changed its practice of registration from notification forms to electronic reporting, mainly through the Danish National Patient Register. The Cancer Registry includes various kinds of information, such as diagnosis, date of diagnosis, topography, and morphology. During the period 1943–1977, cancer diagnoses were coded according to a modified version of the International Classification of Diseases (ICD), 7th revision, which is based primarily on topography [18]. Since 1978, diagnostic information has been coded according to the International Classification of Diseases for Oncology (ICD-O), which is based on topography, morphology, and behavior [15–17]. We categorized all cases of cancer according to Birch and Marsden's International Classification of Childhood Cancer, first edition (ICCC-1), into one of 12 main diagnostic groups, hereafter referred to as 'specific cancer types' [19].

Statistical analyses

Age-specific rates per 100,000 person-years were calculated for all types and specific types of childhood cancer according to birth and calendar year, with the annual Danish population at midyear from the Danish Civil Registration System [20] as the denominator. Age-standardized incidence rates (ASRs) were derived by direct standardization, using the weights of the world standard population (Segi) [21], in order to eliminate changes in the age distribution during the study period and to allow comparison with other countries. ASRs were calculated for any type of childhood cancer overall, and for all specific types of childhood cancer according to calendar year. ASRs were additionally calculated separately for boys and girls. Trends in the incidence of any type and specific types of childhood cancer were quantified by calculating the estimated annual percentage change (EAPC) with corresponding two-sided 95% confidence intervals (95% CI). EAPCs were calculated separately for an early period (1943–1977) and for a recent period (1977–2014), as graphically suggested by the data, by fitting a linear spline regression model with a knot in 1977 to the natural logarithm of the ASRs. For the recent period, EAPCs were additionally calculated separately for 1977–1996 and 1996–2014, to investigate the most recent trends. The weight assigned to each observation was equal to the square of the incidence rate divided by the square of the standard error of the rate. For unspecified malignant neoplasms only, EAPCs were based on two-year periods because of some calendar years having no cases. EAPCs were not calculated for hepatic tumors, as there were too few cases ($n = 133$) for meaningful analysis. Age- and cohort-specific rates were estimated by enumerating number of cases and mid-year population sizes respectively according to age and birth cohort (cohort = year-age) and aggregating according to the categorization of age (0, 1–4, 5–9, 10–14, 15–19) and birth cohort (1943–1949, 1950–1959, 1960–1969, 1970–1979, 1980–1989, 1990–1999, 2000–2014). Incidence rate ratios with corresponding two-sided 95% CIs were used to compare the incidence rates of cancer in two birth cohorts (1943–1949 and 1990–1999) by age group. Statistical analyses were performed with R statistical software, version 3.4.3 (R Development Core Team) and the level of significance was set to 5%.

Results

During the 72-year study period (1943–2014), 15,184 incident childhood cancers were reported, for an average of 211 new cases per year. The average annual number of cases was 168 in the period 1943–1955 which increased to 280 cases in the period 2006–2014 (Table 1). Throughout the study period, childhood cancer was more common in boys than girls, with total numbers of 8,512 male (56.1%) and 6,672 female (43.9%) cases. Overall, the most common cancer type was leukemia (26.5%), followed by central nervous system (CNS) neoplasms (23.4%) and lymphomas (12.9%). From 1986, CNS neoplasms replaced leukemia as the most common cancer type in Danish children and adolescents.

Any type of childhood cancer

Figure 1 shows the ASRs for any type of childhood cancer during the period 1943–2014 for boys, girls and all children. The ASR for any type of childhood cancer increased from 13.0 per 100,000 person-years in the period 1943–1977 to 17.7 per 100,000 person-years in the recent period (Table 2). The EAPC was 0.55% (95% CI 0.30–0.80) for the period 1943–1977 and 1.16% (95% CI 0.96–1.36) for the most recent period, indicating a particularly pronounced increase in the recent period. The increasing trend was seen in both boys and girls in both the early period (EAPC 0.69%; 95% CI 0.43–0.96/EAPC 0.37%; 95% CI −0.01–0.75) and the recent period (EAPC 0.96%; 95% CI 0.75–1.17/EAPC 1.41%; 95% CI 1.11–1.72), although it was most marked for girls in the recent period. Increasing trends were seen for both children aged 0–14 years and adolescents aged 15–19 years, in both the early (EAPC EAPC 0.53%; 95% CI 0.26–0.80/EAPC 0.60%; 95% CI 0.19–1.02) and the recent period (EAPC 0.86%; 95% CI 0.64–1.08/EAPC 1.97%; 95% CI 1.67–2.28). The most pronounced increase in the recent period was observed for the oldest group (15–19 years) (Table 2).

Supplementary Figure 1 shows the age-specific incidence rates by birth cohort. In all birth cohorts, the incidence of cancer was highest in children aged 0–4 and 15–19 years

Table 1. Number of incident childhood cancer cases by sex, age group and cancer type, 1943–2014.

	1943-1955 *n* (%)	1956-1965 *n* (%)	1966-1975 *n* (%)	1976-1985 *n* (%)	1986-1995 *n* (%)	1996-2005 *n* (%)	2006-2014 *n* (%)	Total *n* (%)
Any cancer	2178 (100.0)	1953 (100.0)	2057 (100.0)	2028 (100.0)	2161 (100.0)	2287 (100.0)	2520 (100.0)	15,184 (100.0)
Sex								
Male	1211 (55.6)	1093 (56.0)	1175 (57.1)	1193 (58.8)	1230 (56.9)	1264 (55.3)	1346 (53.4)	8512 (56.1)
Female	967 (44.4)	860 (44.0)	882 (42.9)	835 (41.2)	931 (43.1)	1023 (44.7)	1174 (46.6)	6672 (43.9)
Age group at cancer diagnosis (years)								
<1	169 (7.8)	133 (6.8)	169 (8.2)	112 (5.5)	151 (7.0)	150 (6.6)	158 (6.3)	1042 (6.9)
1-4	680 (31.2)	507 (26.0)	586 (28.5)	473 (23.3)	520 (24.1)	573 (25.0)	553 (21.9)	3892 (25.6)
5-9	431 (19.8)	386 (19.8)	393 (19.1)	394 (19.4)	374 (17.3)	418 (18.3)	415 (16.5)	2811 (18.5)
10-14	396 (18.2)	389 (19.9)	347 (16.9)	417 (20.6)	385 (17.8)	452 (19.8)	470 (18.6)	2856 (18.8)
15-19	502 (23.0)	538 (27.5)	562 (27.3)	632 (31.2)	731 (33.8)	694 (30.3)	924 (36.7)	4583 (30.2)
Cancer type[a]								
Leukemias	708 (32.5)	615 (31.5)	635 (30.9)	499 (24.6)	510 (23.6)	538 (23.5)	526 (20.9)	4,031 (26.5)
Lymphomas	233 (10.7)	260 (13.3)	248 (12.1)	281 (13.8)	264 (12.2)	288 (12.6)	384 (15.2)	1,958 (12.9)
CNS neoplasms	452 (20.8)	420 (21.5)	436 (21.2)	490 (24.2)	562 (26.0)	588 (25.7)	603 (23.9)	3,551 (23.4)
SNS neoplasms	51 (2.3)	72 (3.7)	107 (5.2)	102 (5.0)	102 (4.7)	96 (4.2)	76 (3.0)	606 (4.0)
Retinoblastomas	44 (2.0)	45 (2.3)	46 (2.2)	43 (2.1)	42 (2.0)	48 (2.1)	35 (1.4)	303 (2.0)
Renal tumors	128 (5.9)	78 (4.0)	102 (5.0)	91 (4.5)	82 (3.8)	69 (3.0)	71 (2.8)	621 (4.1)
Hepatic tumors	11 (0.5)	15 (0.8)	19 (0.9)	18 (0.9)	17 (0.8)	20 (0.9)	33 (1.3)	133 (0.9)
Malignant bone tumors	156 (7.2)	114 (5.8)	120 (5.8)	105 (5.2)	93 (4.3)	119 (5.2)	96 (3.8)	803 (5.3)
Soft-tissue sarcomas	149 (6.8)	113 (5.8)	96 (4.7)	89 (4.4)	143 (6.6)	132 (5.8)	163 (6.5)	885 (5.8)
Germ-cell and gonadal tumors	63 (2.9)	78 (4.0)	104 (5.0)	150 (7.4)	161 (7.5)	156 (6.8)	123 (4.9)	835 (5.5)
Malignant epithelial tumors	126 (5.8)	122 (6.2)	121 (5.9)	136 (6.7)	169 (7.8)	209 (9.1)	298 (11.8)	1,181 (7.8)
Unspecified malignant neoplasms	57 (2.6)	21 (1.1)	23 (1.1)	24 (1.2)	16 (0.7)	24 (1.1)	112 (4.5)	277 (1.8)

CNS: central nervous system; SNS: sympathetic nervous system.
[a]Classified according to Birch and Marsden's International Classification of Childhood Cancer, first edition (ICCC-1).

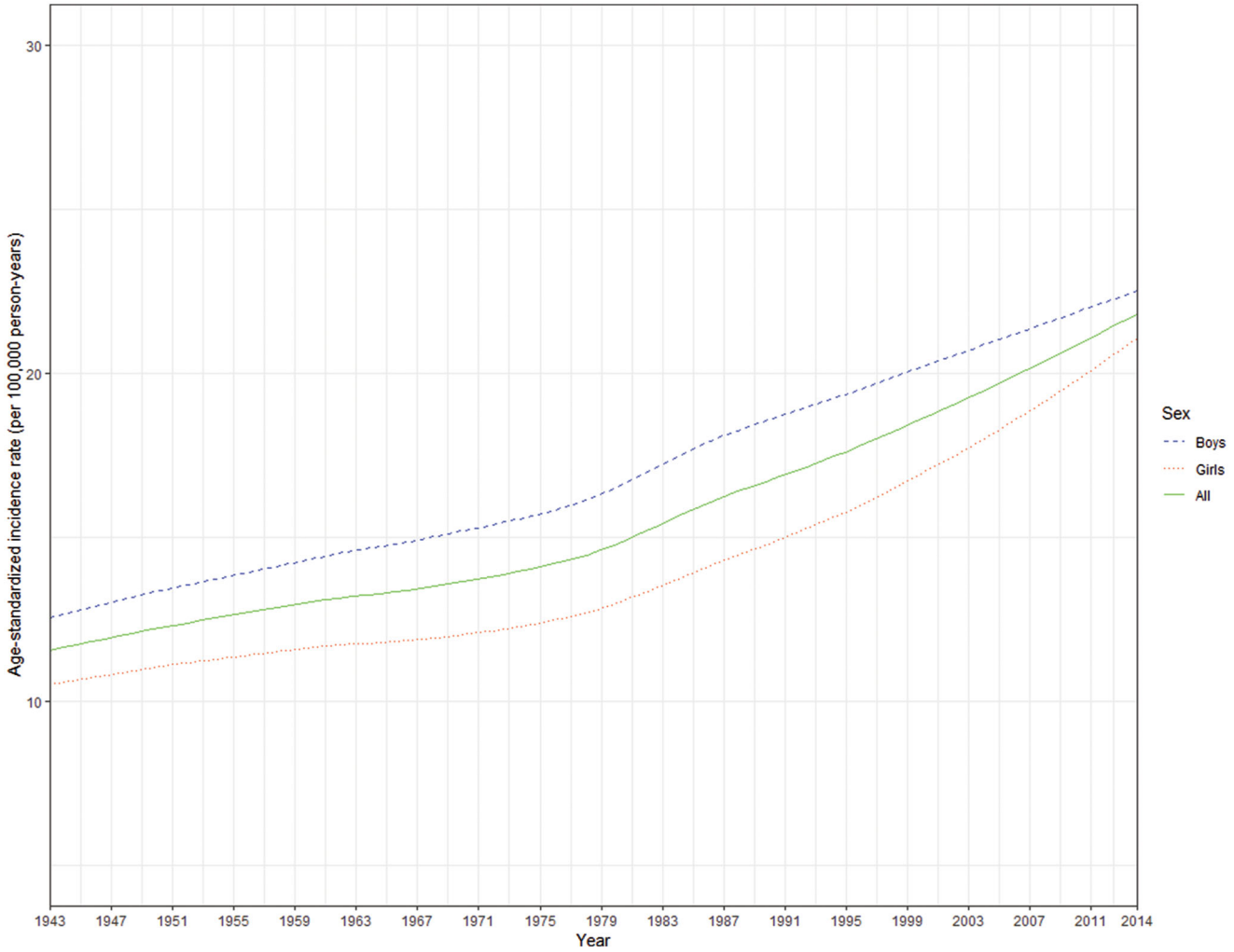

Figure 1. Age-standardized incidence rates (ASRs) for any type of childhood cancer for boys, girls and all children aged 0–19 years in the period 1943–2014.

Table 2. Age-standardized incidence rates (ASRs) and estimated annual percentage change (EAPC) of childhood cancer, 1943–2014.

	Early period (1943–1976)				Recent period (1977–1914)			
	n	ASR[a]	EAPC[b]	(95% CI)	*n*	ASR[a]	EAPC[b]	(95% CI)
Any cancer	6403	13.04	0.55	(0.30;0.80)	8781	17.68	1.16	(0.96;1.36)
Sex								
Male	3608	14.37	0.69	(0.43;0.96)	4904	19.22	0.96	(0.75;1.17)
Female	2795	11.64	0.37	(−0.01;0.75)	3877	16.07	1.41	(1.11;1.72)
Age group (years)								
0–14	4745	12.77	0.53	(0.26;0.80)	5856	16.36	0.86	(0.64;1.08)
15–19	1658	13.97	0.60	(0.19;1.02)	2925	22.22	1.97	(1.67;2.28)
Cancer type[c]								
Leukemias	2007	4.17	−0.01	(−0.48;0.46)	2024	4.38	0.41	(0.00;0.82)
Lymphomas	770	1.50	0.50	(−0.09;1.09)	1188	2.20	1.78	(1.34;2.23)
CNS neoplasms	1366	2.75	1.19	(0.67;1.70)	2185	4.38	1.30	(0.91;1.70)
SNS neoplasms	244	0.53	4.41	(3.28;5.57)	362	0.85	−0.35	(−1.30;0.61)
Retinoblastomas	146	0.33	1.56	(0.18;2.96)	157	0.39	−0.54	(−1.72;0.66)
Renal tumors	318	0.69	1.20	(0.21;2.20)	303	0.71	−0.80	(−1.68;0.10)
Hepatic tumors	47	0.10	–	–	86	0.19	–	–
Malignant bone tumors	397	0.76	−0.63	(−1.50;0.25)	406	0.74	0.49	(−0.29;1.28)
Soft-tissue sarcomas	366	0.74	−0.66	(−1.62;0.30)	519	1.03	2.17	(1.37;2.98)
Germ-cell and gonadal tumors	264	0.52	2.73	(1.59;3.88)	571	1.04	1.53	(0.54;2.52)
Malignant epithelial tumors	376	0.72	−0.27	(−1.12;0.59)	805	1.42	3.74	(3.06;4.42)
Unspecified malignant neoplasms	102	0.21	−4.29	(−6.47;−2.06)	175	0.35	5.87	(3.71;8.08)

CNS: central nervous system; SNS: sympathetic nervous system; CI: confidence interval.
[a]Per 100,000 person-years and standardized according to the world standard population (Segi).
[b]The EAPCs were calculated separately for an early period (1943–1977) and for a recent period (1977–2014), by fitting a linear spline regression model with a knot in 1977 to the natural logarithm of the ASRs.
[c]Classified according to Birch and Marsden's International Classification of Childhood Cancer, first edition (ICCC-1).

and lowest in children aged 5–14 years. Overall, the rate of childhood cancer was higher in younger than older birth cohorts. The incidence rate ratio of cancer in children born in the 1990s as compared with those born in the 1940s were 1.44 (95% CI 1.13–1.85) in infants aged <1 year, 1.27 (95% CI 1.12–1.45) in children aged 1–4 years, 1.37 (95% CI 1.18–1.60) in children aged 5–9 years, 1.51 (95% CI 1.31–1.75) in children aged 10–14 years, and 2.03 (95% CI 1.80–2.28) in those aged 15–19 years.

Specific cancer types

Figure 2 shows the age distribution of cases by childhood cancer type. The leukemia rate peaked at the age of 3 years, with about 10 cases per 100,000 person-years. The incidence of CNS neoplasms was relatively stable at all ages (about 4 cases per 100,000 person-years), in contrast to the incidence of lymphomas, which increased steeply from <0.5 case per 100,000 person-years at the age of 0–3 years to about 5 cases per 100,000 person-years at 19 years of age (Figure 2(a)). The incidence rates of sympathetic nervous system (SNS) neoplasms, retinoblastomas and renal tumors were highest during the first years of life (about 2 cases per 100,000 person-years), whereafter the rates decreased steeply (<0.1 case per 100,000 person-years), especially for retinoblastomas (Figure 2(b)). The rate of malignant bone tumors increased progressively from about 0.1 case per 100,000 person-years in infants <1 year to peak at about 1.7 cases per 100,000 person-years at the age of 16 years. In contrast, the rates of soft-tissue sarcomas and hepatic tumors peaked in infancy, at 0–1 years (about 1.5 cases and 0.6 cases per 100,000 person-years, respectively) (Figure 2(c)). The rates of both germ-cell and gonadal tumors and malignant epithelial tumors peaked late in childhood, at the age of 19 (about 4 and 5 cases per 100,000 person-years, respectively) whereas the rates of unspecified malignant neoplasms were highest for infants (0.5 cases per 100,000 person-years) (Figure 2(d)).

Figure 3 presents ASRs for specific cancer types over time. The incidence of leukemia remained stable during the early period (EAPC −0.01%; 95% CI −0.48–0.46) but increased with 0.41% per year in the recent period (95% CI 0.00–0.82) (Table 2). The incidence rates of lymphomas and CNS neoplasms increased during both the early (EAPC 0.50%; 95% CI −0.09–1.09/EAPC 1.19%; 95% CI 0.67–1.70) and the recent period (EAPC 1.78%; 95% CI 1.34–2.23/EAPC 1.30%; 95% CI 0.91–1.70) but was most pronounced and only statistically significant for lymphomas in the recent period. In contrast, the incidence of SNS neoplasms increased steeply with 4.41% (95% CI 3.28–5.57) per year in the early period and leveled off in the recent period (EAPC −0.35%; 95% CI −1.30–0.61). The incidence of retinoblastomas, renal tumors and malignant bone tumors remained comparatively stable during the study period, although increases were observed for retinoblastomas and renal tumors (EAPC 1.56%; 95% CI 0.18–2.96/EAPC 1.20%; 95% CI 0.21–2.20) in the early period. Increasing incidences of soft-tissue sarcomas and malignant epithelial tumors were observed in the recent period only (EAPC 2.17%; 95% CI 1.37–2.98/EAPC 3.74%; 95% CI 3.06–4.42), whereas the increase in germ-cell and gonadal tumors was seen in both periods (EAPC 2.73%; 95% CI 1.59–3.88/EAPC 1.53%; 95% CI 0.54–2.52). The incidence of hepatic tumors increased steadily from <0.1 to about 0.3 per 100,000 person-years during the study period. In contrast, the incidence of unspecified malignant neoplasms decreased markedly during the early period (EAPC −4.29%; 95% CI −6.47–[−2.06]) and then increased again in the recent period with 5.87% (95% CI 3.71–8.08) per year (Figure 3 and Table 2). In both boys and girls, the increasing trend of any cancer in the recent period was mainly due to an increasing trend in lymphomas, CNS neoplasms, soft-tissue sarcomas

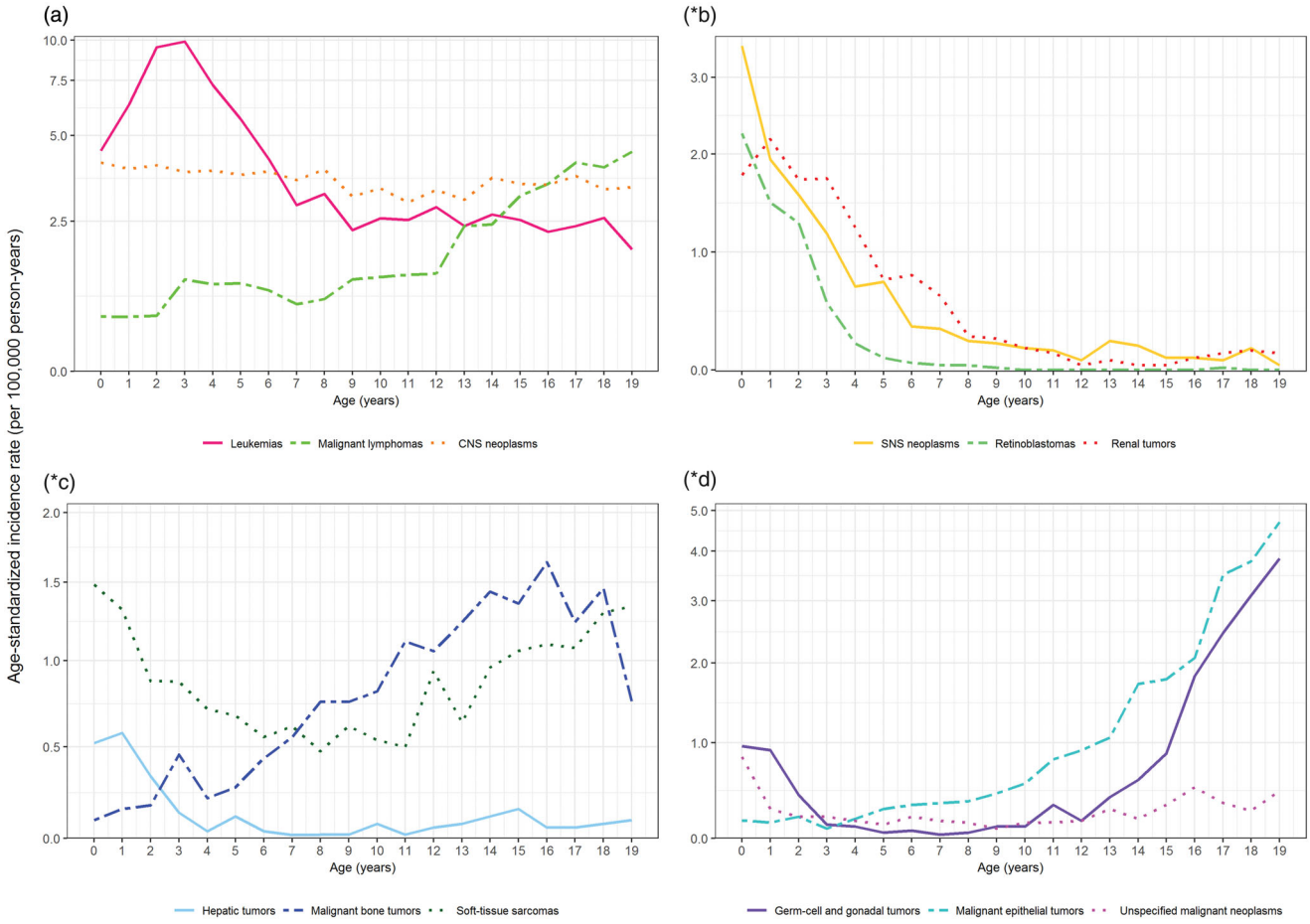

Figure 2. Age-specific incidence rates for the main childhood cancer types in the period 1943–2014. (a) leukemias, lymphomas and central nervous system (CNS) neoplasms, (b) sympathetic nervous system (SNS) neoplasms, retinoblastomas, renal tumors, (c) hepatic tumors, malignant bone tumors, soft-tissue sarcomas, (d) germ-cell and gonadal tumors, malignant epithelial tumors, unspecified malignant neoplasms. *Note different scales on the *y*-axes in the four panels.

and malignant epithelial tumors (Supplementary Tables 1 and 2).

Most recent trends

Although slightly attenuated, in the latest part of the recent period (i.e. 1996–2014) we still saw an increasing trend of any childhood cancer (EAPC 1.06%; 95% CI 0.53–1.59), both in the 0–14 year olds (EAPC 0.73%; 95% CI 0.14–1.32) and the 15–19 years olds (EAPC 1.80%; 95% CI 1.03–2.59) (Supplementary Table 3). In girls, the increasing trend of any childhood cancer became even more pronounced in the latest part of the recent period (EAPC 1.52%; 95% CI 0.71–2.33). The increasing trends of lymphomas (EAPC 2.49%; 95% CI 1.35–3.65), malignant epithelial tumors (EAPC 4.52%; 95% CI 2.73–6.33) and unspecified malignant neoplasms (EAPC 19.60%; 95% CI 14.31–25.14) were particularly pronounced in the latest part of the recent period. Increasing trends were also observed for leukemia (EAPC 0.60%; 95% CI −0.56–1.77), renal tumors (EAPC 1.45%; 95% CI −1.66–4.67), malignant bone tumors (EAPC 0.26%; 95% CI −1.90–2.47) and soft-tissue sarcomas (EAPC 1.19%; 95% CI −0.81–3.22), although non-statistically significant. For all other types of childhood cancer, no increasing trends were observed in this period.

Discussion

We provide the most comprehensive description and analysis of the incidence and time trends of childhood cancer in Denmark over 72 consecutive years, based on high-quality data. We found a statistically significant increase in the incidence rate of any type of childhood cancer, with an estimated annual increase of 0.55% in 1943–1977 and 1.16% in 1977–2014, respectively. The increasing trend was seen in young children (0–14 years) and adolescents (15–19 years) and in both sexes in both periods. The most pronounced increase was seen in the recent period for older children, with a 1.97% increase per year, and in girls, among whom the incidence rate increased by 1.41% per year. For specific childhood cancer types, increasing trends were seen in the early period mainly in SNS neoplasms, retinoblastomas, and renal tumors and in the recent period for leukemias, lymphomas, soft-tissue sarcomas and malignant epithelial tumors. The incidence rates of CNS and germ-cell and gonadal tumors increased in both periods, while the incidence of unspecified malignant neoplasms decreased in the early period and then increased steeply in the recent period. The increasing trend of childhood cancer was still evident in the latest part of the recent period (1996–2014) most pronounced among girls and for lymphomas, epithelial tumors and the unspecified malignant neoplasms.

Figure 3. Age-standardized incidence rates (ASRs) for the main childhood cancer types by calendar year in the period 1943–2014. (a) Leukemias, lymphomas and central nervous system (CNS) neoplasms, (b) sympathetic nervous system (SNS) neoplasms, retinoblastomas, renal tumors, (c) hepatic tumors, malignant bone tumors, soft-tissue sarcomas, (d) germ-cell and gonadal tumors, malignant epithelial tumors, unspecified malignant neoplasms. *Note different scales on the *y*-axes in the four panels.

International comparisons

Throughout the study period the three most common cancer types in Danish children were leukemias, CNS neoplasms and lymphomas, as observed in other Nordic and European countries and the USA. After 1986, CNS neoplasms became more frequent than leukemias also in line with other reports [22].

In comparison with the most recent European (ASR in the 1990s: 15.7 per 100,000 person-years) [10] and global data (ASR in the 2000s: 15.6 per 100,000 person-years) [11], the incidence of any cancer in children in Denmark is among the highest in the world (ASR in the period 1977–2014: 17.7 per 100,000 person-years). The Danish ASR is, however, similar to those in several other high-income countries: Sweden (16.2 per 100,000 person-years, 1990–2011), Norway (18.2 per 100,000 person-years, 1990–2013), Iceland (17.0 per 100,000 person-years, 1990–2014), Germany (17.0 per 100,000 person-years, 1994–2012), Australia (17.5 per 100,000 person-years, 1992–2014), Canada (17.6 per 100,000 person-years, 1992–2013) and the USA (non-Hispanic whites 19.1 per 100,000 person-years, 1998–2012). The ASR of childhood cancer is, however, somewhat higher in Denmark than in England (14.5 per 100,000 person-years, 1990–2013) [22].

In line with our finding of an increasing incidence of any type of cancer in children in the recent period (EAPC 1977–2014: 1.16%), a Danish study in 2006 reported an annual increase of about 1% in the period 1970–1999 [7]. Increasing trends in the incidence of any childhood cancer have also been reported in several other countries in Europe and globally [10,11,13,23]. Two older Danish studies reported slight increases in the overall incidence of childhood cancer in boys, but not in girls during the period 1943–1980s [5,6], consistent with our finding of a relatively small increasing trend (0.55% per year) in the early period (1943–1977) mostly seen in boys (0.69% per year). In the more recent period, however, the increasing trend was higher among girls (1.41% per year) than boys (0.96% per year). A similar tendency was observed in a study of European children [13]. In both periods, the increasing trend was stronger in the group of older children compared to younger children. Similar results were reported in a study of European children and adolescents, where a more pronounced increasing trend was seen among children aged 15–19 years (1.5% per year) compared to younger children (1% per year) [10].

With regard to specific cancer types in the recent period, we observed ASRs (per 100,000 person-years) of 4.38 for leukemia and 2.20 for lymphoma, fairly similar to those reported in Europe, North America and Australia during the 1990s and 2000s [22]. The ASRs for CNS neoplasms were higher in Denmark (4.38) than in Australia (2.35), England (2.62),

Germany (3.01), and Canada (3.08) but comparable to those in Sweden (3.71), Iceland (4.01), and the USA (4.29). In contrast, the ASR was higher in Norway (4.91). The ASRs for the remaining childhood cancer types were similar to those in Sweden, Norway, Iceland, Germany, England, Australia, Canada and the USA, except for malignant epithelial tumors, for which the ASRs were somewhat higher in Iceland (2.35) and Australia (2.50) than in Denmark (1.42) [22].

We observed increasing time trends for the most common childhood cancer types, namely leukemias, lymphomas, and CNS neoplasms in the most recent period. A similar pattern was observed during 1970–1999 in a European study [10]. In contrast, stable trends in all childhood cancer types were observed among white children in the USA during 2001–2009 [24]. Also in line with the results from the European study, we observed increasing trends for soft-tissue sarcomas, germ-cell and gonadal tumors, and malignant epithelial tumors in the recent period. In contrast to the European study, however, we observed stable trends in SNS neoplasms, renal tumors, retinoblastomas, and malignant bone tumors in the recent period, whereas the authors of the other study found indications of increasing trends for these cancer types [10]. We could not calculate a trend for hepatic tumors, but the ASR increased from 0.10 in the early period to 0.19 per 100,000 children in the recent period, similar to the increasing trend in hepatic tumors observed in Europe during 1970–1999 [10]. We observed a marked decrease in the incidence of unspecified malignant neoplasms in the early period but a substantial increase in the recent period, which might partially be due to Danish legislation that resulted in fewer autopsies, the rate decreasing from 45% in 1970 to 16% in the second half of 1990 [25].

Strength and limitations

Major strengths of this study are the longstanding, high-quality data in the Danish Cancer Registry and the exceptionally long study period. The nationwide population-based Danish Cancer Registry enables analysis of virtually complete data on childhood cancer dating back more than seven decades. The availability of information from multiple sources (hospital departments, general practitioners, practicing specialists, autopsy reports, and death certificates) increases the validity of the Registry, and the data on incident cancers are of high quality, with an estimated completeness of 95–98% [14–17]. Coding for registration in the Registry has always been supervised by medical doctors [15,17], increasing the validity of the coding of different cancers. Furthermore, since 1968, computerized checks have been conducted for logical errors such as unusual or rare combinations of sex, morphology, stage, and treatment, since full digitalization of the Registry [15–17]. In addition, from the mid-1940s to the beginning of the 1990s, the proportion of histologically confirmed cancers in the Registry increased from 54.9% to 93.1%, and the proportion of diagnoses based only on death certificates decreased from 18.5% to 0.7% [15]. Supervision of coding, computerized checks, a large number of histologically verified cancers, and the few cancers identified solely from death certificates enhance the validity of this study.

Although the validity of childhood cancer diagnoses has been improved by the larger proportion of histologically confirmed cancers, computerized checks and lower proportion of cancers identified from death certificates only, these changes may have affected the trends observed. However, increasing trends were observed in separate time periods with more comparable cancer registration procedures. Furthermore, increasing trends were also observed in the latest part of the recent period (i.e. after the changes in registration practice), therefore these changes are unlikely to fully explain the increasing trends observed.

In 1978, the Danish Cancer Registry changed its coding system from ICD-7 to ICD-O, which could potentially affect the registration and classification of childhood cancers. However, no changes were made to the criteria of notifications to the registry [7]. Furthermore, childhood cancers cases have been reevaluated for the period 1943–1977, by applying an ICD-O code based on original information from pathologists and clinicians [5]. Hence, this change in reporting to the Danish Cancer Registry is not expected to have had a significant impact on our results.

Before 1987, reporting to the Danish Cancer Registry was voluntary, which could have resulted in underreporting of cancer cases during this period. Nevertheless, medical doctors were not only encouraged by the Danish Medical Association to report cases to the Registry but, before 1987, were also paid a fee for each completed notification, supplying an economic incentive [15,17]. Notifications from multiple sources ensure the completeness of the Registry, also before 1987. Storm *et al.* concluded that the change from voluntary to mandatory notification had no effect on the number of cases reported [15]. Hence, changes to the notification practice appear unlikely to explain the increasing incidence found, as supported by our findings of increasing trends both before and after 1987.

Improved diagnostic methods due to neuroimaging could result in an artefactual increase in CNS neoplasms. Computed tomography was introduced in Denmark in the mid-1970s [26], however, we observed increasing trends for CNS neoplasms in both the early and the recent period, suggesting that improved diagnostics with neuroimaging cannot explain the increase entirely. Furthermore, the finding of a simultaneous increase in mortality due to CNS neoplasms in Danish children indicates that the increase may be real [26]. An increasing trend in any childhood cancer was still found after exclusion of CNS neoplasms in calculating ASR, further demonstrating that the increase in childhood cancer incidence cannot be explained solely by improved neuroimaging.

Potential underlying causes

Established risk factors, such as high doses of ionizing radiation, chemotherapeutic agents [3], or specific chromosomal and genetic abnormalities (e.g. Down syndrome,

neurofibromatosis, ataxia-telangiectasia), explain only a small percentage of all childhood cancer cases [27]. It has been suggested that the increased incidence of childhood cancer is, to some extent, a result of changes in yet unknown lifestyle or environmental exposures [2,3]. Studies implicating modern lifestyle elements such as the use of fertility treatment, increasing parental age, and maternal use of hormonal contraception may indicate important directions for further research into the etiology of childhood cancer [28–30].

Conclusion

The incidence of childhood cancer in Denmark has increased since the 1940s, especially since 1977, in older children and in girls. The increasing trends in the incidence of several childhood cancer types other than CNS neoplasms suggests that the increase is likely to reflect a true increase in risk. To clarify possible reasons for this increase, studies focusing on changes in factors that may be responsible for the development of or the protection against cancer in children are needed.

Disclosure statement

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