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Temporal trends in incidence of childhood cancer in Switzerland, 1985–2014

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ABSTRACT

Background: Incidence of childhood cancer increased in most countries worldwide, but reasons are unclear. This study investigates trends of childhood cancer incidence in Switzerland from 1985 to 2014.
Methods: We extracted data on all childhood cancer cases diagnosed at ages 0–14 years in Switzerland from the Swiss Childhood Cancer Registry. We included ICCC-3 main groups I-XII and calculated age-standardised, cumulative, and age-specific incidence for different diagnostic groups. We analysed trends of annual age-standardised incidence using JoinPoint regression models.
Results: Over the study period from 1985 to 2014, 5104 of 5486 cancer diagnoses (93%) were microscopically verified. The proportion of children treated in paediatric cancer centres increased from 84% during 1985–1994 to 93% in 1995–2004 and 98% in 2005–2014 ($p < 0.001$). Using the World standard population, age-standardised incidence was 143 in 1985–1994, 154 in 1995–2004, and 162 per million in 2005–2014. Incidence increased by 0.7% (95% confidence interval (CI) 0.5; 1.0) per year for all cancers from 1985 to 2014, 0.8% (95% CI 0.2%–1.4%) for leukaemias over the same period, 3.0% (95% CI 0.2%–1.4%) for CNS tumours during 1985–2002, and 3.8% (95% CI 1.7%–6.0%) for epithelial neoplasms and melanomas over the period 1985–2014.
Conclusion: Trends in incidence were driven mostly by increases among leukaemias and CNS tumours. For CNS tumours, observed trends may be explained at least partially by diagnostic changes and improved registration. For leukaemias, rising incidence may be real and due to risk factors that experience similar increases in trends.

1. Introduction

Incidence of childhood cancer increased in Europe by 11% from 1991 to 2010 [1]. The reasons for this increase remain unclear. Improved case ascertainment and diagnostics could account for this trend [2,3], or the trend could represent a real increase in cancer risks [4–7]. Most countries have seen increasing trends in childhood cancers, though results vary by reporting period and cancer type [2] [7–19]. Switzerland is one of the few countries with a national childhood cancer registry that has been in existence for over 40 years [20]. However, registry data on incidence of childhood cancer have only been published for the diagnostic period 1995–2005 [21,22]. Trends in the incidence of childhood cancer over a period of 30 years from 1985 to 2014 have not yet been analysed.

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This study is the first to assess long-term trends in incidence of childhood cancer in Switzerland. The two major aims are: to calculate age-standardised, age-specific, and cumulative incidence for three diagnostic periods—1985–1994, 1995–2004, and 2005–2014—and to describe trends in age-standardised incidence over the entire period from 1985 to 2014. We also assessed indices of quality of registered cases in the SCCR.

2. Methods

2.1. Study population and procedure

The Swiss Childhood Cancer Registry (SCCR) was founded by the Swiss Paediatric Oncology Group (SPOG) in 1976 and initially registered patients included in clinical trials [20]. Beginning in 1981, all patients treated in paediatric cancer centres were systematically included. In a retrospective study, covering the period 1990–2004, we discovered, however, 16% of children with cancer had not been treated in paediatric cancer centres, including infants who were diagnosed only at autopsy in neonatal departments [23].

Between 2004 and 2007, the SCCR was reorganized according to international recommendations [24,25], and the review of diagnoses using pathology reports, quality indices, and retrospective inclusion of missed cases were introduced. Since then, the SCCR improved case completeness by comparing datasets with the population based cancer registries of each Swiss canton, and by finding missed cases in mortality statistics [26]. The SCCR calculated the proportion of cases that came to its attention only by death certificate notification and found that completeness increased from 85% in 1985 to 95% since 1995 [26].

A clinical research coordinator in each paediatric cancer centre notifies the SCCR of new cases within two months of diagnosis. Children diagnosed with cancer before they reach the age of 16 years, and older adolescents diagnosed with typical paediatric tumours are usually treated in paediatric cancer centres at Aarau, Basel, Bellinzona, Bern, Geneva, Lausanne, Lucerne, St. Gallen, and Zurich.

For this study, we included all children with Swiss residency at diagnosis who were registered in the SCCR, and diagnosed with cancer according to one of the 12 main diagnostic groups of the ICCC-3 at ages 0–14 years between 1 st January 1985 and 31 st December 2014.

2.2. Measurements

The SCCR registers patients with leukaemias and lymphomas, malignant and benign CNS tumours, malignant solid tumours, and Langerhans cell histiocytosis who were diagnosed at ages under 21 years in Switzerland. The registry records personal information including name, sex, date of birth, address, nationality; diagnostic information including exact diagnosis and its date, basis of diagnosis, site and grade of primary and subsequent tumour(s), histological type and grade, immunophenotype and genetics, stage at diagnosis, laterality, and site of any metastasis; and treatment information that includes the name and type of treating institution, treatment type, study type, and study protocol name. Diagnoses are classified according to the International Classification of Diseases, tenth revision (ICD-10); topography and morphology of the ICD for Oncology, third revision (ICD-O-3); and the International Classification of Childhood Cancer, third edition (ICCC-3) [24,27,28]. The study was covered by the Ethics Committee of the Canton of Bern approval to the SCCR (KEK-BE: 166/2014).

2.3. Statistical methods

We calculated incidence rates based on population data from the Swiss Federal Statistical Office [29]. To assess indices of quality, we identified cancers treated in paediatric cancer centres and cancers that had microscopically verified diagnoses that were confirmed from histology of a primary tumour, haematological examination of peripheral blood or bone marrow, or histology of metastasis. We then calculated the average number of cases diagnosed per year and the proportional distribution of ICCC-3 main groups during the three decades 1985–1994, 1995–2004, and 2005–2014. We calculated incidence rates (IR) for ICCC-3 main groups and subgroups per decade expressed per million children [24], with direct standardization for age using the World standard population [30]. We calculated cumulative IR, defined as the sum of age-specific IR over each year of age from 0 to 14 years and the risk of being diagnosed with cancer before the age of 15 years (1 divided by the cumulative IR). We also computed age-specific IRs for the age groups < 1, 1–4, 5–9, and 10–14 years. The 95% confidence intervals (95% CI) for the IR were calculated assuming Poisson distribution. We used R version 3.2.2 for data preparation, descriptive statistics, and calculation of IRs.

We examined trends in annual age-standardised incidence ratios from 1985 to 2014 for all diagnostic groups combined, separately for boys and girls, and for main diagnostic groups. For explorative purposes, we have also calculated trends for subgroups, for instance by age groups and diagnostic subgroups of leukaemias, lymphomas and CNS tumours, and split by sex. We used JoinPoint, Version 4.0.2.2, assessing the magnitude and direction of trends over time and quantifying the average annual percentage change (AAPC) [10,12,15,18,31–34]. JoinPoint fitted straight regression lines through the data, with the natural logarithm of age-standardised incidence rates as dependent variable and calendar year (1985–2014) as independent variable. We used a maximum of two joinpoints to detect a maximum of three different trends, with a minimum of three years between joinpoints. We selected the trend lines that provided the best fit to observed age-standardised incidence rates, based on the ratio of the sums of squared errors from the null model and the alternative model. Inference is conducted through Monte Carlo permutation tests as implemented in the software [32].

The study population included 98 patients (2%) who were registered from death certificate notifications. We had no information on ICCC-3 main group for 12 of these and lacked dates of diagnosis for 75. We classified patients with missing diagnosis as having had other malignant neoplasms and imputed date of diagnosis with the missforest package for R [35]. To generate the missing values we used observed data for year of birth, sex, cancer diagnosis and age at death in the imputation model. We excluded the 98 cases from all analyses using the specific subgroups of ICCC-3 cancer diagnoses (Supplemental Table 1).

3. Results

In 2014, Switzerland had a population of 7.825 million inhabitants, of which 1.225 million were aged 0–14 years. from 1985 to 2014, the SCCR registered 5486 cancer cases in children aged 0–14 years living in Switzerland (Supplemental Fig. 1). Of those, 5104 (93%) were microscopically verified (Table 1). The proportion of verified cases of leukaemias has remained at 100% since 1995. Microscopic verification of cancer was highest in 1995–2004 and then decreased again in 2005–2014. This was due to decreases in CNS tumours, retinoblastomas, and renal tumours.

The proportion of cancers treated in paediatric cancer centres increased from 84% during 1985–1994 to 98% for 2005–2014 (Supplemental Table 2). The increase was largest for CNS tumours and epithelial neoplasms & melanomas; the proportion of CNS tumours treated in paediatric cancer centres increased from 71% in 1985–1994 to 98% in 2005–2014.

During 1985–1994, 1673 of the registered cancer cases had been diagnosed at age 0–14 years; 1880 cases were diagnosed in 1995–2004 and 1933 cases in 2005–2014 (Table 1). In all three decades, the most common cancers were leukaemias (33%), CNS tumours (22%), and lymphomas (12%) (Supplemental Table 3). Among leukaemia diagnoses, 17 patients had Down syndrome in the period from 1985 to

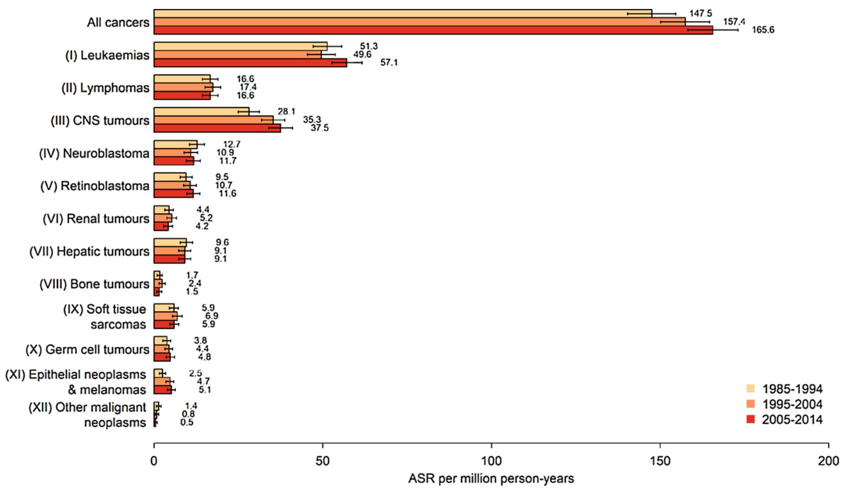

Fig. 1. Comparison of incidence of childhood cancer between 1985–1994, 1995–2004 and 2005–2014, by cancer diagnosis. Abbreviations: ASR, Age-standardized incidence rate. Cancer diagnoses were classified according to the International Classification of Childhood Cancer, third edition (ICCC-3). Incidence rates were age-standardized according to the World standard population. Error bars show 95% confidence intervals.

1994, 25 from 1995–2004 and 18 from 2005–2014. Very few were second leukaemias; two from 1985–1994, two from 1995–2004, and four from 2005–2014 (data not shown). The overall annual age-standardised incidence rate per million children rose from 147 for 1985–1994 to 166 during 2005–2014 (Table 2, Fig. 1). Age-standardised incidence in all three decades was highest for leukaemias, CNS tumours, and lymphomas, and the overall cumulative incidence before the age of 14 years rose from 2135 to 2423 per million children from 1985–1994 to 2005–2014.

Childhood cancer was more common in boys than in girls, with a male to female ratio of 1.28 during 2005–2014 (Table 2). The male to female ratio was largest for Burkitt's lymphoma, 6.71, and smallest for thyroid carcinomas, 0.27 (Supplemental Table 1). Among all childhood cancers diagnosed until age 14 years, leukaemias had the highest age-specific incidence rate between age 1-4 years, lymphomas between 10-14 years and CNS tumours between 5-9 years. Cancer diagnoses in which incidence rates were highest at age < 1 year were neuroblastoma, retinoblastoma, renal tumours, hepatic tumours, germ cell tumours and other malignant tumours (Table 3).

Overall, age-standardised childhood cancer incidence increased between 1985–2014 by 0.7% per year (95% CI 0.4%–1.0%), though trends differed between age groups, type of cancer, and sex (Table 4, Fig. 2, Supplemental Table 4). This increase was highest for children diagnosed between the ages of 10 and 14 years. The annual increase of 0.8% (95% CI 0.1%–1.4%) from 1985 to 2014 for the incidence of leukaemias was mainly driven by a 1.2% (95% CI 0.3%–2.1%) increase among lymphoid leukaemias, particularly in boys (Supplemental Table 4b). The incidence of CNS tumours increased annually by 3.0% (95% CI 1.4%–4.7%) from 1985 to 2002, but not thereafter (Table 4). Over the entire period, to 2014, the annual increase was 1.4% (95% CI 0.4%–2.4%) for boys and 1.7% (95% CI 0.6%–2.7%) for girls. Incidence of epithelial neoplasms and melanomas increased by 3.7% (95% CI 1.6%–5.8%) from 1985 to 2014, but because they account for only 3% of all cancer cases (165 of 5486 total cases) this had a very small effect on the overall trend (Tables 1 and 4).

Table 1
Numbers of incident cancers and proportions of microscopically verified cancers among all children diagnosed with cancer in Switzerland at age 0–14 years from 1985 to 2014, by diagnostic period.

	1985-1994				1995-2004				2005-2014				
	All cases	Microscopically verified[a]	%	95% CI	All cases	Microscopically verified[a]	%	95% CI	All cases	Microscopically verified[a]	%	95% CI	p-value[b]
All cancers (N = 5486)	1673	1539	92.0	90.7; 93.3	1880	1769	94.1	93.0; 95.2	1933	1796	92.9	91.8; 94.1	0.047
Age at diagnosis													
0-4 years	804	727	90.4	88.4; 92.5	825	754	91.4	89.5; 93.3	830	755	91.0	89.0; 92.9	0.792
5-9 years	444	410	92.3	89.9; 94.8	498	475	95.4	93.5; 97.2	509	472	92.7	90.5; 95.0	0.112
10-14 years	425	402	94.6	92.4; 96.7	557	540	96.9	95.5; 98.4	594	569	95.8	94.2; 97.4	0.182
ICCC-3 Main diagnostic group													
I. Leukaemias	569	561	98.6	97.6; 99.6	581	581	100		647	647	100		< 0.001
II. Lymphomas	201	200	99.5	98.5; 99.9	225	225	100		214	213	99.5	98.6; 99.9	0.580
III. CNS tumours	328	275	83.8	79.9; 87.8	429	376	87.6	84.5; 90.8	448	364	81.3	77.6; 84.9	0.033
IV. Neuroblastoma	134	117	87.3	81.7; 92.9	115	106	92.2	87.3; 97.1	119	112	94.1	89.9; 98.3	0.147
V. Retinoblastoma	46	19	41.3	27.1; 55.5	53	17	32.1	19.5; 44.6	42	6	14.3	3.7; 24.9	0.020
VI. Renal tumours	102	99	97.1	93.8; 99.9	98	97	99.0	97.0; 99.9	98	92	93.9	89.1; 98.6	0.135
VII. Hepatic tumours	18	12	66.7	44.9; 88.4	27	27	100		16	15	94	81.9; 99.9	0.002
VIII. Bone tumours	73	71	97	93.5; 99.9	95	95	100		79	79	100		0.091
IX. Soft tissue sarcomas	111	110	99	97.3; 99.9	129	128	99.2	97.7; 99.9	139	139	100		0.555
X. Germ cell tumours	45	42	93.3	86.0; 99.9	53	52	98.1	94.5; 99.9	57	56	98.2	94.8; 99.9	0.303
XI. Epithelial neoplasms & melanomas	31	29	93.5	84.9; 99.9	65	63	96.9	92.7; 99.9	69	69	100		0.140
XII. Other malignant neoplasms	15	4	26.7	4.3; 49.0	10	2	20.0	0.0; 44.8	5	4	80	44.9; 99.9	0.055

Abbreviations: CI, confidence interval; CNS, central nervous system; ICCC-3, International Classification of Childhood Cancer, third edition.
[a] Includes histology of primary tumours and metastasis, and cytology.
[b] p-value derived from Kruskal-Wallis rank sum test for trend, comparing the numbers of microscopically verified cases between the three time periods.

Table 2
Incidence of childhood cancer in Switzerland at age 0–14 years from 1985 to 2014, by diagnostic group and period.

1985-1994	Average number of cases/year (%)	ASR per million population/year (95% CI)[a]	CR per million population (95% CI)[b]	1:N children[c]	Male/ Female[d]
All cancers	166.6 (100)	147.5 (140.3; 154.6)	2135.3 (2108.8; 2161.8)	468	1.24
ICCC-3 Main diagnostic group					
I. Leukaemias	56.9 (34.2)	51.3 (47.1; 55.6)	730.3 (714.8; 745.8)	1369	1.29
II. Lymphomas	20.1 (12.1)	16.6 (14.3; 18.9)	259.2 (249.9; 268.4)	3858	2.14
III. CNS tumours	32.4 (19.4)	28.1 (25.0; 31.2)	417.1 (405.4; 428.8)	2398	1.17
IV. Neuroblastoma	13.4 (8.0)	12.7 (10.5; 14.9)	168.9 (161.4; 176.3)	5921	1.27
V. Retinoblastoma	4.6 (2.8)	4.4 (3.2; 5.7)	58.0 (53.6; 62.4)	17241	0.84
VI. Renal tumours	10.2 (6.1)	9.6 (7.7; 11.4)	129.8 (123.3; 136.4)	7704	0.76
VII. Hepatic tumours	1.8 (1.1)	1.7 (0.9; 2.4)	22.9 (20.1; 25.6)	43668	1.25
VIII. Bone tumours	7.3 (4.4)	5.9 (4.5; 7.2)	94.3 (88.7; 99.9)	10604	1.03
IX. Soft tissue sarcomas	10.9 (6.5)	9.5 (7.7; 11.3)	139.6 (132.8; 146.3)	7163	1.06
X. Germ cell tumours	4.4 (2.6)	3.8 (2.6; 4.9)	56.4 (52.1; 60.7)	17730	1.10
XI. Epithelial neoplasms & melanomas	3.1 (1.9)	2.5 (1.6; 3.4)	39.9 (36.3; 43.5)	25063	1.07
XII. Other malignant neoplasms	1.5 (0.9)	1.4 (0.7; 2.1)	19.1 (16.6; 21.6)	52356	0.88

1995-2004	Average number of cases/year (%)	ASR per million population/year (95% CI)[a]	CR per million population (95% CI)[b]	1:N children[c]	Male/ Female[d]
All cancers	187.5 (100)	157.4 (150.2; 164.6)	2298.9 (2272.2; 2325.6)	435	1.27
ICCC-3 Main diagnostic group					
I. Leukaemias	57.8 (30.8)	49.6 (45.5; 53.7)	710.3 (695.4; 725.1)	1408	1.40
II. Lymphomas	22.5 (12.0)	17.4 (15.1; 19.7)	270.6 (261.4; 279.7)	3695	1.81
III. CNS tumours	42.9 (22.9)	35.3 (31.9; 38.7)	523.4 (510.6; 536.1)	1911	1.25
IV. Neuroblastoma	11.3 (6.0)	10.9 (8.9; 12.9)	144.6 (137.9; 151.3)	6916	0.92
V. Retinoblastoma	5.3 (2.8)	5.2 (3.8; 6.6)	68.4 (63.7; 73.0)	14620	0.96
VI. Renal tumours	9.8 (5.2)	9.1 (7.3; 10.9)	122.5 (116.3; 128.6)	8163	1.00
VII. Hepatic tumours	2.7 (1.4)	2.4 (1.5; 3.3)	33.9 (30.6; 37.1)	29499	3.50
VIII. Bone tumours	9.5 (5.1)	6.9 (5.5; 8.3)	112.8 (106.9; 118.7)	8865	0.94
IX. Soft tissue sarcomas	12.9 (6.9)	10.7 (8.8; 12.5)	157.7 (150.7; 164.7)	6341	1.48
X. Germ cell tumours	5.3 (2.8)	4.4 (3.2; 5.5)	65.1 (60.6; 69.5)	15361	0.77
XI. Epithelial neoplasms & melanomas	6.5 (3.5)	4.7 (3.5; 5.8)	77.5 (72.5; 82.4)	12903	0.81
XII. Other malignant neoplasms	1.0 (0.5)	0.8 (0.3; 1.3)	12.3 (10.4; 14.3)	81301	1.00

2005-2014	Average number of cases/year (%)	ASR per million population/year (95% CI)[a]	CR per million population (95% CI)[b]	1:N children[c]	Male/ Female[d]
All cancers	192.4 (100)	165.6 (158.2; 173.1)	2423.4 (2395.5; 2451.2)	413	1.28
ICCC-3 Main diagnostic group					
I. Leukaemias	64.3 (33.4)	57.1 (52.7; 61.6)	816.0 (799.8; 832.2)	1225	1.57
II. Lymphomas	21.3 (11.1)	16.6 (14.4; 18.9)	262.4 (253.2; 271.5)	3811	1.77
III. CNS tumours	44.5 (23.1)	37.5 (34.0; 41.0)	560.7 (547.3; 574.1)	1783	1.17
IV. Neuroblastoma	11.9 (6.2)	11.7 (9.6; 13.7)	153.0 (146.0; 160.0)	6536	1.13
V. Retinoblastoma	4.2 (2.2)	4.2 (2.9; 5.4)	54.1 (49.9; 58.3)	18484	0.83
VI. Renal tumours	9.7 (5.0)	9.1 (7.3; 10.9)	124.4 (118.1; 130.7)	8039	0.80
VII. Hepatic tumours	1.6 (0.8)	1.5 (0.8; 2.3)	20.4 (17.9; 23.0)	49020	1.67
VIII. Bone tumours	7.9 (4.1)	5.9 (4.6; 7.3)	97.1 (91.5; 102.7)	10299	0.88
IX. Soft tissue sarcomas	13.9 (7.2)	11.6 (9.7; 13.6)	173.9 (166.5; 181.4)	5750	1.36
X. Germ cell tumours	5.7 (3.0)	4.8 (3.6; 6.1)	71.0 (66.2; 75.8)	14085	1.19
XI. Epithelial neoplasms & melanomas	6.9 (3.6)	5.1 (3.9; 6.3)	84.0 (78.8; 89.2)	11905	0.60
XII. Other malignant neoplasms	0.5 (0.3)	0.5 (0.1; 0.9)	6.3 (4.9; 7.7)	158730	1.50

Abbreviations: ASR, age-standardised incidence rate; CI, confidence interval; CNS, central nervous system; CR, cumulative incidence rate; ICCC-3, International Classification of Childhood Cancer, third edition.
[a]Standardised according to the World standard population.
[b]Cumulative incidence up to the age of 14 years.
[c]Number of children affected up to the age of 14 years in Switzerland.
[d]Male:female ratio.

Table 3
Age-specific incidence rate per million population in Switzerland and average cases per year from 2005 to 2014, by age at diagnosis and diagnostic group.

	Age-specific incidence rate (95% CI)				Average cases per year per million population			
Age at cancer diagnosis	< 1 year	1-4 years	5-9 years	10-14 years	< 1 year	1-4 years	5-9 years	10-14 years
All cancers	228.3 (195.9; 264.6)	209.5 (193.7; 226.3)	129.7 (118.6; 141.5)	142.0 (130.8; 154.0)	11.8	43.4	33.7	39.4
ICCC-3 Main diagnostic group								
I. Leukaemias	36.1 (24.0; 52.2)	99.1 (88.4; 110.8)	43.9 (37.6; 51.0)	32.7 (27.4; 38.7)	1.9	20.5	11.4	9.1
II. Lymphomas	3.9 (0.8; 11.3)	9.7 (6.5; 13.8)	14.9 (11.3; 19.3)	29.3 (24.4; 35.0)	0.2	2.0	3.9	8.1
III. CNS tumours	36.1 (24.0; 52.2)	38.3 (31.7; 45.8)	40.6 (34.5; 47.4)	33.6 (28.3; 39.7)	1.9	7.9	10.5	9.3
IV. Neuroblastoma	65.8 (49.0; 86.5)	18.7 (14.2; 24.1)	1.5 (0.6; 3.4)	1.0 (0.3; 2.5)	3.4	3.9	0.4	0.3
V. Retinoblastoma	25.8 (15.8; 39.8)	6.4 (3.9; 9.9)	0.5 (0.1; 1.9)	0.0 (0.0; 0.7)	1.3	1.3	0.1	0.0
VI. Renal tumours	18.1 (9.9; 30.3)	16.7 (12.5; 21.9)	6.4 (4.2; 9.5)	1.4 (0.5; 3.1)	0.9	3.5	1.7	0.4
VII. Hepatic tumours	7.7 (2.8; 16.8)	2.3 (0.9; 4.6)	0.5 (0.1; 1.9)	0.2 (0.0; 1.3)	0.4	0.5	0.1	0.1
VIII. Bone tumours	0.0 (0.0; 3.9)	1.6 (0.5; 3.8)	5.6 (3.5; 8.6)	12.5 (9.3; 16.4)	0.0	0.3	1.5	3.5
IX. Soft tissue sarcomas	11.6 (5.3; 22.0)	12.6 (8.9; 17.2)	9.2 (6.5; 12.8)	13.2 (10.0; 17.2)	0.6	2.6	2.4	3.7
X. Germ cell tumours	19.4 (10.8; 31.9)	3.5 (1.8; 6.3)	1.8 (0.7; 3.7)	5.8 (3.7; 8.6)	1.0	0.7	0.5	1.6
XI. Epithelial neoplasms & melanomas	1.3 (0.0; 7.2)	0.3 (0.0; 1.8)	4.4 (2.5; 7.0)	12.0 (8.9; 15.8)	0.1	0.1	1.1	3.3
XII. Other malignant neoplasms	2.6 (0.3; 9.3)	0.3 (0.0; 1.8)	0.3 (0.0; 1.4)	0.2 (0.0; 1.3)	0.1	0.1	0.1	0.1

Abbreviations: CI, confidence interval; CNS, central nervous system; ICCC-3, International Classification of Childhood Cancer, third edition.

4. Discussion

We report age-standardised, age-specific and cumulative incidence of childhood cancer for the three diagnostic periods 1985–1994, 1995–2004 and 2005–2014 in Switzerland. Overall cancer incidence rates significantly increased between 1985–2014, mainly driven by leukaemias and CNS tumours. The trend for CNS tumours plateaued in the 2000s, but continued for leukaemias and epithelial neoplasms & melanomas. The increase in overall incidence rates was age-dependent, with no increase in pre-school children up to 4 years, a slight increase in children 5–9 years old, and a stronger increase in young adolescents 10–14 years old.

4.1. International comparison

The proportion of microscopically verified cases in the SCCR is high (> 93%), suggesting excellent validity of cancer diagnoses. This is comparable to validity ranging from 92 to 98% reported in other European countries [16,36,11,37,38,10], and in Japan (90%) [39], the US (95%) [31] and Australia (97%) [12]. Lower proportions of microscopically verified cases in certain tumours do not necessarily mean lower data quality, though. They could be due to treatment changes or to improved detection methods of some cancer diagnoses without surgery. For retinoblastoma, current treatment rarely involves surgical removal of the eye, which has led to a decreasing proportion of microscopically verified cases from 41% for 1985–1994 to 14% during 2005–2014. Patients with low-grade gliomas and certain high grade tumours are increasingly diagnosed with imaging techniques if they are in regions where biopsy puts the patient at high risk for functional loss. This is reflected in a decreasing proportion of microscopically verified CNS tumours from 92% during 1985–1994 to 82% during 2005–2014.

Supplemental Table 5 compares the relative distribution of diagnostic groups and the overall age-standardised incidence of childhood cancer in Switzerland to the Piedmont region in Italy [10], Spain [11], Sweden [8], France [36], Germany [7], Austria [16], Europe combined [1], USA [51], Canada [40], Australia [12], and Korea [13]. The relative distribution of diagnostic groups was similar to these countries, but age-standardized leukaemia incidence was among the highest, with higher values only observed in Sweden, Germany, and Australia, and incidence of neuroblastoma was among the lowest except Sweden and Australia.

We observed that overall cancer incidence rates in Switzerland continuously rose over the whole study period, from 1985 to 2014. Overall incidence rates increased in all world regions except sub-Saharan Africa from the 1980s to 2001–2010 [37], but remained stable in Austria [16], Ireland [17], the USA [18], Canada [15], and Australia [12] in more recent time periods (Supplemental Table 6). The increased incidence of childhood cancer observed in our study is mainly attributable to leukaemia and CNS tumours. Incidence of leukaemia increased steadily until 2014, without evidence of a plateau. Most countries also observed an increase [2,6–8,10–13,17,19], while studies from the USA and Austria reported stable leukaemia incidence [16,18,31] (Supplemental Table 6). Leukaemia incidence in Canada first increased but levelled off after 1999 [15]. We observed that incidence of CNS tumours increased until 2002 and plateaued thereafter, similar to Australia [12]. Many studies found increases over the entire study period [1,7,10,11,16,19], others found no increase [13,15,18,31,34,41,42] or even a decrease [34]. We also found that incidence of epithelial neoplasms and melanomas increased over the entire study period, similar to the USA [9,31], Australia [12], and Korea [13]. Some of the observed trends in cancer incidence may perhaps be due to slight changes of regional coverage of the registries.

4.2. Possible reasons for increasing trend in incidence

The increased incidence of childhood cancer may be attributable to several factors. First, improved case registration would increase the observed incidence. Patients with CNS tumours, with epithelial neoplasms & melanomas and aged 10–14 years at time of cancer diagnosis increasingly have been treated in paediatric oncology centres. These paediatric oncology centres collaborate closely with the SCCR and actively report every newly diagnosed child [24]. Since 1985, SCCR coverage has improved from 85% to 95% [26]. The SCCR has retrospectively registered missed cases, but we cannot exclude that some of the children with CNS tumours or children treated in earlier decades in adult facilities escaped registration, and thus that earlier incidence of childhood cancers is underestimated. Advances in medical diagnostics also may have increased apparent incidence rates. Imaging techniques have enhanced the capacity to diagnose otherwise undetected low-grade CNS tumours since the mid-1980s [2,43]. Finally, medical and environmental risk factors could have increased the incidence of some cancers, including leukaemias, in particular, which recently increased in nearly all countries. Leukaemia and CNS tumours may be associated with exposure to low-level ionizing radiation [44], which has likely increased in recent decades due to the increasing use of imaging techniques that rely upon ionizing radiation, especially computed tomography [45]. This might explain the age-dependent pattern of increase. Increasing parental age is an established risk factor for childhood leukaemias, which could also

Table 4
Average annual percentage change (AAPC) in incidence rates of childhood cancer standardized according to the World standard population, by diagnostic group, age and sex in Switzerland 1985–2014: Results from JoinPoint regression.

	Trend 1		Trend 2	
Diagnostic group	Period	AAPC (95% CI)	Period	AAPC (95% CI)
All cancers	1985–2014	**0.7 (0.4; 1.0)**		
0-4 years	1985–2014	0.3 (−0.1; 0.7)		
5-9 years	1985–2014	**0.8 (0.2; 1.3)**		
10-14 years	1985–2014	**1.4 (0.9; 2.0)**		
I. Leukaemias	1985–2014	**0.8 (0.1; 1.4)**		
II. Lymphomas	1985–2014	−0.1 (−1.0; 0.9)		
III. CNS tumours	1985–2002	**3.0 (1.4; 4.7)**	2002–2014	−0.3 (−2.5; 2.1)
IV. Neuroblastoma	1985–2014	−0.4 (−1.6; 0.8)		
V. Retinoblastoma	1985–2014	−0.9 (−3.0; 1.3)		
VI. Renal tumours	1985–2014	−0.4 (−1.6; 0.8)		
VII. Hepatic tumours	1985–2014	n.a.		
VIII. Bone tumours	1985–2014	0.2 (−1.0; 1.4)		
IX. Soft tissue sarcomas	1985–2014	0.9 (−0.5; 2.3)		
X. Germ cell tumours	1985–2014	1.6 (−0.1; 3.4)		
XI. Epithelial neoplasms & melanomas	1985–2014	**3.7 (1.6; 5.8)**		
XII. Other malignant neoplasms	1985–2014	n.a.		
Boys				
All cases	1985–2014	**0.8 (0.4; 1.2)**		
I. Leukaemias	1985–2014	**1.2 (0.3; 2.1)**		
II. Lymphomas	1985–2014	−0.1 (−1.1; 0.9)		
III. CNS tumours	1985–2014	**1.4 (0.4; 2.4)**		
IV. Neuroblastoma	1985–2014	−1 (−2.2; 0.2)		
V. Retinoblastoma	1985–2014	n.a.		
VI. Renal tumours	1985-2014	0 (-1.9; 2.0)		
VII. Hepatic tumours	1985–2014	n.a.		
VIII. Bone tumours	1985–2014	n.a.		
IX. Soft tissue sarcomas	1985–2014	0.5 (−1.0; 2.1)		
X. Germ cell tumours	1985–2014	n.a.		
XI. Epithelial neoplasms & melanomas	1985–2014	n.a.		
XII. Other malignant neoplasms	1985–2014	n.a.		
Girls				
All cases	1985–2014	**0.6 (0.2; 1.0)**		
I. Leukaemias	1985–2014	0.1 (−0.6; 0.9)		
II. Lymphomas	1985–2014	−0.1 (−2.0; 1.9)		
III. CNS tumours	1985–2014	**1.7 (0.6; 2.7)**		
IV. Neuroblastoma	1985–2014	0.7 (−1.3; 2.7)		
V. Retinoblastoma	1985–2014	n.a.		
VI. Renal tumours	1985–2014	−0.7 (−2.5; 1.0)		
VII. Hepatic tumours	1985–2014	n.a.		
VIII. Bone tumours	1985–2014	0.6 (−1.1; 2.4)		
IX. Soft tissue sarcomas	1985–2014	n.a.		
X. Germ cell tumours	1985–2014	n.a.		
XI. Epithelial neoplasms & melanomas	1985–2014	n.a.		
XII. Other malignant neoplasms	1985–2014	n.a.		

Abbreviations: AAPC, average annual percentage change; CI, confidence interval; CNS, central nervous system; n.a., not applicable.
Bold letters indicate AAPCs with p-values < 0.

explain part of the observed increasing trend in incidence [46]. Other factors that might have contributed to the increasing incidence include exposure to infections [47] and to pesticides [48]. However, there is limited data to support these hypotheses. Traffic-related air pollution [49] and parental exposure to benzene [50] and background radiation [44] are unlikely to have contributed, because trends were decreasing or stable over time in Switzerland. However, the results of this study do not allow us to draw conclusions about specific risk factors that may have contributed to the overall increasing incidence of cancer in general, and specifically of leukaemia and CNS tumours.

4.3. Strengths and limitations of the study

The nationwide, population-based coverage of the SCCR with a high completeness of registration is a real strength of this study [26]. Data quality was high with an average of 93% of the cases being microscopically verified. For CNS tumours and retinoblastomas, the percentage of microscopically verification decreased over time, reflecting changes in the standards of diagnosing childhood cancer. We could include recent diagnostic years (until 2014) due to the fast reporting and quality control procedures in the SCCR [20]. For the most recent years, the SCCR is in the process of exchanging data with the cantonal cancer registries. Therefore, we may have underestimated increases in incidence in the most recent period, although the SCCR missed very few cases in previous linkages. The sample size was limited by the comparatively small population of Switzerland, which led to wide confidence intervals for some diagnostic groups, particularly for diagnostic subgroups of childhood cancer. Thus results should be interpreted cautiously because trends may reflect random fluctuations in incidence.

5. Conclusions

Changes in registration procedures and advances in medical diagnostics may explain the increase observed in the incidence in CNS tumours. For leukaemia, rising incidence may be real and due to risk factors that experience similar increases in trends. Future aetiological research should examine these long-term trends together with changes in medical and environmental risk factors.

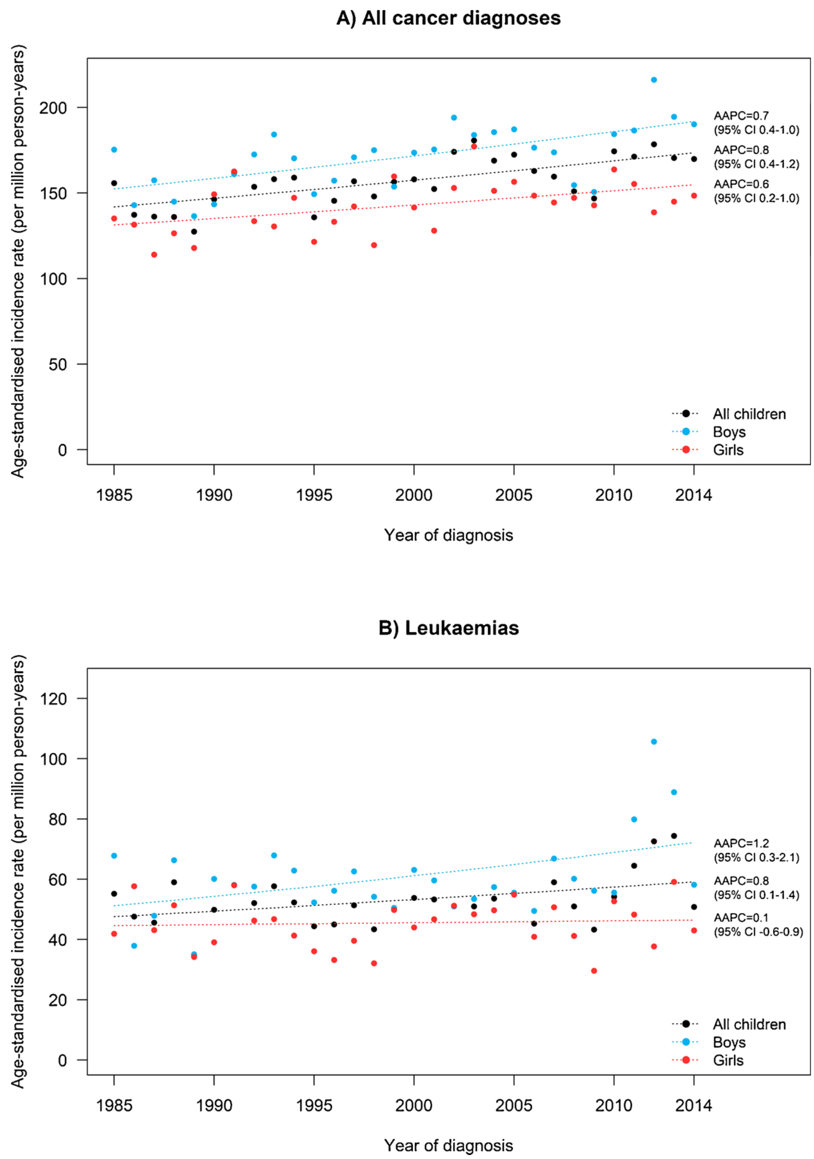

Fig. 2. Trends in incidence rates (per million person-years) in Switzerland between 1985 and 2014, standardized according to the World standard population, for A) all childhood cancer diagnoses combined and B) leukaemias. Trends were modelled using JoinPoint regression.
Abbreviations: AAPC, average annual percentage change; CI, confidence interval.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.06.002.

References

[1] E. Steliarova-Foucher, M.M. Fidler, M. Colombet, B. Lacour, P. Kaatsch, M. Pineros, I. Soerjomataram, F. Bray, J.W. Coebergh, R. Peris-Bonet, C.A. Stiller, A. contributors, Changing geographical patterns and trends in cancer incidence in children and adolescents in Europe, 1991–2010 (automated childhood cancer information system): a population-based study, Lancet Oncol. 19 (2018) 1159–1169.
[2] M.E. Kroll, L.M. Carpenter, M.F. Murphy, C.A. Stiller, Effects of changes in diagnosis and registration on time trends in recorded childhood cancer incidence in Great

Britain, Br J Cancer 107 (2012) 1159–1162.
[3] P. Adamson, G. Law, E. Roman, Assessment of trends in childhood cancer incidence, Lancet 365 (2005) 753.
[4] R.J. McNally, D.P. Cairns, O.B. Eden, A.M. Kelsey, G.M. Taylor, J.M. Birch, Examination of temporal trends in the incidence of childhood leukaemias and lymphomas provides aetiological clues, Leukemia 15 (2001) 1612–1618.
[5] R.J. McNally, A.M. Kelsey, D.P. Cairns, G.M. Taylor, O.B. Eden, J.M. Birch, Temporal increases in the incidence of childhood solid tumors seen in Northwest England (1954-1998) are likely to be real, Cancer 92 (2001) 1967–1976.
[6] M.E. Kroll, G.J. Draper, C.A. Stiller, M.F. Murphy, Childhood leukemia incidence in Britain, 1974–2000: time trends and possible relation to influenza epidemics, J Natl. Cancer Inst. 98 (2006) 417–420.
[7] C. Spix, D. Eletr, M. Blettner, P. Kaatsch, Temporal trends in the incidence rate of childhood cancer in Germany 1987–2004, Int. J Cancer 122 (2008) 1859–1867.
[8] A.C. Dreifaldt, M. Carlberg, L. Hardell, Increasing incidence rates of childhood malignant diseases in Sweden during the period 1960–1998, Eur J Cancer 40 (2004) 1351–1360.
[9] E.M. Ward, M.J. Thun, L.M. Hannan, A. Jemal, Interpreting cancer trends, Ann. N Y Acad. Sci. 1076 (2006) 29–53.
[10] E. Isaevska, M. Manasievska, D. Alessi, M.L. Mosso, C. Magnani, C. Sacerdote, G. Pastore, F. Fagioli, F. Merletti, M. Maule, Cancer incidence rates and trends among children and adolescents in piedmont, 1967-2011, PLoS One 12 (2017) e0181805.
[11] R. Peris-Bonet, D. Salmeron, M.A. Martinez-Beneito, J. Galceran, R. Marcos-Gragera, S. Felipe, V. Gonzalez, J. Sanchez de Toledo Codina, Childhood cancer incidence and survival in Spain, Ann. Oncol. 21 (Suppl. 3) (2010) iii103-10.
[12] P.D. Baade, D.R. Youlden, P.C. Valery, T. Hassall, L. Ward, A.C. Green, J.F. Aitken, Trends in incidence of childhood cancer in Australia, 1983-2006, Br J Cancer 102 (2010) 620–626.
[13] H.J. Park, E.K. Moon, J.Y. Yoon, C.M. Oh, K.W. Jung, B.K. Park, H.Y. Shin, Y.J. Won, Incidence and survival of childhood cancer in korea, Cancer Res. Treat. (2016), https://doi.org/10.4143/crt.2015.290.
[14] R. Zheng, X. Peng, H. Zeng, S. Zhang, T. Chen, H. Wang, W. Chen, Incidence, mortality and survival of childhood cancer in China during 2000-2010 period: A population-based study, Cancer Lett. 363 (2015) 176–180.
[15] D. Mitra, A.K. Shaw, K. Hutchings, Trends in incidence of childhood cancer in Canada, 1992-2006, Chronic Dis. Inj. Can. 32 (2012) 131–139.
[16] H.E. Karim-Kos, M. Hackl, G. Mann, C. Urban, A. Woehrer, I. Slavc, R. Ladenstein, Trends in incidence, survival and mortality of childhood and adolescent cancer in Austria, 1994-2011, Cancer Epidemiol 42 (2016) 72–81.
[17] National cancer registry Ireland, Cancer Trends (2014).
[18] D.A. Siegel, J. King, E. Tai, N. Buchanan, U.A. Ajani, J. Li, Cancer incidence rates and trends among children and adolescents in the United States, 2001-2009, Pediatrics 134 (2014) e945–55.
[19] F. Pesola, J. Ferlay, P. Sasieni, Cancer incidence in English children, adolescents and young people: past trends and projections to 2030, Br J Cancer 117 (2017) 1865–1873.
[20] V. Pfeiffer, S. Redmond, R. Kuonen, G. Sommer, B. Spycher, M. Schindler, P. Singh, G. Michel, C. Kuehni, Swiss Childhood Cancer Registry - Annual Report 2014/2015, Institute of Social and Preventive Medicine, University of Bern, Switzerland, 2015.
[21] G. Michel, N.X. von der Weid, M. Zwahlen, M. Adam, C.E. Rebholz, C.E. Kuehni, swiss childhood cancer R, swiss paediatric oncology group scientific C. The swiss childhood cancer registry: rationale, organisation and results for the years 2001-2005, Swiss Med. Wkly. 137 (2007) 502–509.
[22] G. Michel, N.X. von der Weid, M. Zwahlen, S. Redmond, M.P. Strippoli, C.E. Kuehni, Swiss Paediatric Oncology G, Incidence of childhood cancer in Switzerland: the swiss childhood cancer registry, Pediatr Blood Cancer 50 (2008) 46–51.
[23] M. Adam, N. von der Weid, G. Michel, M. Zwahlen, J.M. Lutz, N. Probst-Hensch, F. Niggli, C. Kuehni, swiss pediatric oncology G, swiss association of cancer R. Access to specialized pediatric cancer care in Switzerland, Pediatr Blood Cancer 54 (2010) 721–727.
[24] E. Steliarova-Foucher, C. Stiller, B. Lacour, P. Kaatsch, International classification of childhood cancer, 3rd ed, Cancer 103 (2005) 1457–1467.
[25] O.M. Jensen, D.M. Parkin, R. MacLennan, C.S. Muir, R.G. Skeet, Cancer Registration: Principles and Methods, IARC Sci Publ, 1991.
[26] M. Schindler, V. Mitter, E. Bergstraesser, F. Gumy-Pause, G. Michel, C.E. Kuehni, Death certificate notifications in the swiss childhood cancer registry: assessing completeness and registration procedures, Swiss Med. Wkly. 145 (2015) w14225.
[27] A. Fritz, C. Percy, A. Jack, K. Shanmugaratnam, L. Sobin, D. Parkin, S. Whelan, International Classification of Diseases for Oncology, 3rd ed., World Health Organisation, Geneva, 2000.
[28] World Health Organisation, International Statistical Classification of Diseases and Related Health Problems, 10th Revision. Geneva (1992).
[29] Swiss Federal Statistical Office, Population and Households Statistics (STATPOP), (2016) http://www.bfs.admin.ch/bfs/portal/de/index/news/02/03/01/01.html.
[30] M. Segi, S. Fujisaku, M. Kurihara, Y. Narai, K. Sasajima, The age-adjusted death rates for malignant neoplasms in some selected sites in 23 countries in 1954-1955 and their geographical correlation, Tohoku J Exp. Med. 72 (1960) 91–103.
[31] A.M. Linabery, J.A. Ross, Trends in childhood cancer incidence in the U.S. (1992-2004), Cancer 112 (2008) 416–432.
[32] National Cancer Institute, Joinpoint Trend Analysis Software, (2016) http://surveillance.cancer.gov/joinpoint/.
[33] J.L. Barrington-Trimis, M. Cockburn, C. Metayer, W.J. Gauderman, J. Wiemels, R. McKean-Cowdin, Trends in childhood leukemia incidence over two decades from 1992 to 2013, Int. J Cancer 140 (2017) 1000–10008.
[34] P. Papathoma, T.P. Thomopoulos, M.A. Karalexi, A. Ryzhov, A. Zborovskaya, N. Dimitrova, S. Zivkovic, S. Eser, L. Antunes, M. Sekerija, T. Zagar, J. Bastos, A. Demetriou, R. Cozma, D. Coza, E. Bouka, N. Dessypris, M. Kantzanou, P. Kanavidis, H. Dana, E. Hatzipantelis, M. Moschovi, S. Polychronopoulou, A. Pourtsidis, E. Stiakaki, E. Papakonstantinou, K. Oikonomou, S. Sgouros, A. Vakis, B. Zountsas, C. Bourgioti, N. Kelekis, P. Prassopoulos, T. Choreftaki, S. Papadopoulos, K. Stefanaki, K. Strantzia, E. Cardis, E. Steliarova-Foucher, E.T. Petridou, Childhood central nervous system tumours: incidence and time trends in 13 Southern and Eastern European cancer registries, Eur J Cancer 51 (2015) 1444–1455.
[35] D.J. Stekhoven, P. Buhlmann, MissForest–non-parametric missing value imputation for mixed-type data, Bioinformatics 28 (2012) 112–118.
[36] B. Lacour, A. Guyot-Goubin, S. Guissou, S. Bellec, E. Desandes, J. Clavel, Incidence of childhood cancer in France: national children cancer registries, 2000-2004, Eur J Cancer Prev. 19 (2010) 173–181.
[37] E. Steliarova-Foucher, M. Colombet, L.A.G. Ries, F. Moreno, A. Dolya, F. Bray, P. Hesseling, H.Y. Shin, C.A. Stiller, Contributors I-. International incidence of childhood cancer, 2001-10: a population-based registry study, Lancet Oncol. (2017), https://doi.org/10.1016/S1470-2045(17)30186-9.
[38] P. Kaatsch, C. Spix, German Childhood Cancer Registry - Report 2013/14 (1980-2013), Institute of Medical Biostatistics, Epidemiology and Informatics (IMBEI) at the University Medical Center of the Johannes Gutenberg University Mainz, Germany, 2014.
[39] K. Katanoda, A. Shibata, T. Matsuda, M. Hori, K. Nakata, Y. Narita, C. Ogawa, W. Munakata, A. Kawai, H. Nishimoto, Childhood, adolescent and young adult cancer incidence in Japan in 2009-2011, Jpn. J Clin. Oncol. (2017) 1–10, https://doi.org/10.1093/jjco/hyx070.
[40] L. Ellison, T. Janz, Childhood Cancer Incidence and Mortality in Canada: Statistics Canada, (2015).
[41] L.S. Schmidt, K. Schmiegelow, P. Lahteenmaki, C. Trager, T. Stokland, K. Grell, G. Gustafson, A. Sehested, O. Raashou-Nielsen, C. Johansen, J. Schuz, Incidence of childhood central nervous system tumors in the nordic countries, Pediatr Blood Cancer 56 (2011) 65–69.
[42] L. Fairley, S.V. Picton, R.J. McNally, S. Bailey, M.G. McCabe, R.G. Feltbower, Incidence and survival of children and young people with central nervous system embryonal tumours in the North of England, 1990-2013, Eur J Cancer 61 (2016) 36–43.
[43] M.A. Smith, B. Freidlin, L.A. Ries, R. Simon, Trends in reported incidence of primary malignant brain tumors in children in the United States, J Natl. Cancer Inst. 90 (1998) 1269–1277.
[44] B.D. Spycher, J.E. Lupatsch, M. Zwahlen, M. Roosli, F. Niggli, M.A. Grotzer, J. Rischewski, M. Egger, C.E. Kuehni, swiss pediatric oncology G, swiss national cohort study G. Background ionizing radiation and the risk of childhood cancer: a census-based nationwide cohort study, Environ. Health Perspect 123 (2015) 622–628.
[45] D.L. Miglioretti, E. Johnson, A. Williams, R.T. Greenlee, S. Weinmann, L.I. Solberg, H.S. Feigelson, D. Roblin, M.J. Flynn, N. Vanneman, R. Smith-Bindman, The use of computed tomography in pediatrics and the associated radiation exposure and estimated cancer risk, Jama Pediatrics 167 (2013) 700–707.
[46] R. Wang, C. Metayer, L. Morimoto, J.L. Wiemels, J. Yang, A.T. DeWan, A. Kang, X. Ma, Parental age and risk of pediatric cancer in the offspring: A population-based record-linkage study in California, Am J Epidemiol 186 (2017) 843–856.
[47] C. Kreis, E. Doessegger, J.E. Lupatsch, B.D. Spycher, Space-time clustering of childhood cancers: a systematic review and pooled analysis, Eur J Epidemiol 34 (2019) 9–21.
[48] M. Chen, C.H. Chang, L. Tao, C. Lu, Residential exposure to pesticide during childhood and childhood cancers: A meta-analysis, Pediatrics 136 (2015) 719–729.
[49] B.D. Spycher, M. Feller, M. Roosli, R.A. Ammann, M. Diezi, M. Egger, C.E. Kuehni, Childhood cancer and residential exposure to highways: a nationwide cohort study, Eur J Epidemiol 30 (2015) 1263–1275.
[50] B.D. Spycher, J.E. Lupatsch, A. Huss, J. Rischewski, C. Schindera, A. Spoerri, R. Vermeulen, C.E. Kuehni, Parental occupational exposure to benzene and the risk of childhood cancer: A census-based cohort study, Environ. Int. 108 (2017) 84–91.
[51] United States Department of Health and Human Services CfDCaPaNCI. United States Cancer Statistics: 1999-2013 Incidence, WONDER Online Database. 2016.