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Cause-specific long-term mortality in survivors of childhood cancer in Switzerland: A population-based study

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Survivors of childhood cancer have a higher mortality than the general population. We describe cause-specific long-term mortality in a population-based cohort of childhood cancer survivors. We included all children diagnosed with cancer in Switzerland (1976–2007) at age 0–14 years, who survived ≥5 years after diagnosis and followed survivors until December 31, 2012. We obtained causes of death (COD) from the Swiss mortality statistics and used data from the Swiss general population to calculate age-, calendar year-, and sex-standardized mortality ratios (SMR), and absolute excess risks (AER) for different COD, by Poisson regression. We included 3,965 survivors and 49,704 person years at risk. Of these, 246 (6.2%) died, which was 11 times higher than expected (SMR 11.0). Mortality was particularly high for diseases of the respiratory (SMR 14.8) and circulatory system (SMR 12.7), and for second cancers (SMR 11.6). The pattern of cause-specific mortality differed by primary cancer diagnosis, and changed with time since diagnosis. In the first 10 years after 5-year survival, 78.9% of excess deaths were caused by recurrence of the original cancer (AER 46.1). Twenty-five years after diagnosis, only 36.5% (AER 9.1) were caused by recurrence, 21.3% by second cancers (AER 5.3) and 33.3% by circulatory diseases (AER 8.3). Our study confirms an elevated mortality in survivors of childhood cancer for at least 30 years after diagnosis with an increased proportion of deaths caused by late toxicities of the treatment. The results underline the importance of clinical follow-up continuing years after the end of treatment for childhood cancer.

Cancer is the second most common cause of death in children in developed countries.[1,2] Improvements in childhood cancer therapies have drastically increased survival over the past decades, and 5-year survival rates now exceed 80%.[3–6] Unfortunately, about two thirds of childhood cancer survivors experience late effects from the cancer or its treatment; about a third of these effects are severe or life threatening.[7,8] The leading causes of death for children who have survived 5-years after diagnosis are recurrence or progress of the original cancer, second cancers, and non-neoplastic diseases, for example, of the circulatory or respiratory system.[9–13] Clinical studies are generally designed for assessing efficacy of treatment protocols typically up to 5 up or 10 years from diagnosis. Several studies have shown that survivors of childhood cancer are not followed systematically into adulthood.[14,15] Epidemiological studies are therefore necessary to

Key words: childhood cancer, cancer survivors, mortality, second primary cancers, cardiovascular, respiratory, causes of death, cancer registry

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What's new?

As survivors of childhood cancer age, they are more likely to die prematurely than their peers. The causes of early death, however, are not fully understood, particularly for recently diagnosed children, who may benefit from newer treatment strategies. This study shows that for at least three decades after diagnosis, childhood cancer survivors suffer increased mortality. Disease recurrence initially accounts for the greatest proportion of deaths but is supplanted over time by late treatment-related toxicities, including second cancers. The findings draw attention to the significance of lifelong follow-up among survivors of childhood cancer, especially for high-risk individuals.

monitor long-term mortality on the population level. Although there are studies on cause-specific long-term mortality at the population level in the United States, and in Europe,[10,11,16–25] few could include recently diagnosed children.[9,12] As treatment modalities have changed over the past decades, studies should include younger cohorts of survivors who have benefited from newer treatment regimens.[26]

We used data from the Swiss Childhood Cancer Registry (SCCR) (i) to compare overall and cause-specific mortality of childhood cancer survivors to that of the general population in Switzerland and describe associated factors, and (ii) describe cumulative mortality after 5-year survival for different causes of death and different diagnostic periods.

Methods

Patient cohort

The study cohort consisted of all 5-year survivors of childhood cancer diagnosed before age 15 between January 1, 1976 and December 31, 2007 in Switzerland. Data came from the population-based Swiss Childhood Cancer Registry (SCCR).[27,28] Recent estimates suggest that it includes 91% (about 95% since 1995) of all childhood cancer cases diagnosed in Switzerland.[29] The SCCR has access to medical records of patients and codes the primary cancer diagnosis in childhood according to the International Classification of Childhood Cancer (ICCC), 3rd edition.[30]

Ascertaining cause of death

We obtained coded causes of death by linking records with mortality statistics in Switzerland.[31] The COD statistics always includes the underlying COD and, if available, one consecutive, and up to two contributing causes of death, as coded by the Swiss Federal Statistical Office (SFSO). SFSO coded causes of death according to the International Classification of Diseases, 8th revision (ICD-8) for deaths before 1995, and according to the 10th revision (ICD-10) for deaths after 1995.[32,33] For each death, we asked the SFSO for a copy of the original death certificate. Death certificates also contain notes and remarks about a death, which are not always possible to be classified by the ICD of the corresponding period. Medical personnel of the SCCR had information on date, site, morphology, treatment and recurrence/progression of the original cancer diagnosis, and examined death certificates. The most probable cause of death from a clinical point of view was assessed and compared with the officially underlying cause of death from mortality statistics. If the clinical cause of death was different from the official cause of death, we used the clinical cause of death, and coded it based on the ICD of the corresponding period. Otherwise we used the official cause of death and its ICD code. We classified coded cause of death into the following subgroups: recurrence or progression of the primary cancer; second cancers; circulatory diseases; respiratory diseases; infectious and parasitic diseases; other medical causes of death; and, external causes of death.

Statistical methods

Examination of long-term mortality for all cohort members started 5 years after their first childhood cancer was diagnosed and continued until date of death, loss-to-follow-up, or December 31, 2012, whichever came first. We calculated standardized mortality ratios (SMR) and absolute excess risks (AER) overall and for specific causes of death. SMR and AER were age- (1-year band), calendar year (1-year band)- and sex-standardized using Swiss mortality rates as obtained from the SFSO. SMR was defined as the ratio of observed deaths divided by the number of expected deaths. AER was defined as the observed number of deaths minus the expected number of deaths, divided by the number of person-years at risk, and expressed by 10,000 person-years. Because there are no deaths from recurrence the general population, we only report crude mortality rates for this cause of death. We stratified SMR and AER by sex, age at diagnosis ($<$1 year, 1–4, 5–9 and 10–14 years), treatment era (1976–1983, 1984–1991, 1992–1999, 2000–2007) recurrence within 5 years from diagnosis (no/yes), radiotherapy (no/yes), chemotherapy (no/yes), HSCT (no/autologous/allogeneic), years from diangosis ((5–14, 15–24, $\geq$ 24), attained age in years (0–19, 20–29, 30–39, 40–49, $\geq$50) and type of childhood cancer. For the all causes combined we further stratified ICCC-3 main groups into subgroups (acute lymphatic leukaemia [ALL], acute myeloid leukaemia [AML], Hodgkin- and non-Hodgkin lymphoma, ependymomas, astrocytomas, primitive neuroectodermal tumors [PNET], medulloblastomas, osteosarcomas, Ewing sarcomas, rhabdomyosarcomas and other soft-tissue sarcomas). If data for a variable was missing, we grouped the missing values in an additional category. We estimated the simultaneous effect of these factors on risk of death from all causes of death, from recurrence and from second cancers using multivariable Poisson regression models that included all variables. We estimated cumulative mortality (CM) as a

Table 1. Life status, standardized mortality ratios (SMR) and absolute excess risks (AER) for 5-year survivors of childhood cancer diagnosed at age 0–14 years between 1976 and 2007 (SMR and AER are standardized according to age-, sex-, and calendar year)

	Eligible Cohort	All causes of death				Recurrent/progressive disease[1]		2nd cancer[1]		
		PY	Obs/Exp	SMR	AER[2]	Obs	Crude rate[3]	Obs/Exp	SMR	AER[2]
All patients	3965	49703.9	246/22.3	11.0 (9.7-12.5)	45.0 (39.6-52)	153	30.9 (26.4-36.2)	32/2.8	11.6 (8.2-16.4)	5.9 (4.0-8.5)
Sex										
Male	2215	27838.6	142/16.7	8.5 (7.2-10.0)	45.0 (37.9-54.8)	87	31.3 (25.4-38.7)	18/1.6	11.0 (6.9-17.4)	5.9 (3.5-9.7)
Female	1750	21865.4	104/5.6	18.4 (15.2-22.4)	45.0 (36.8-55.2)	66	30.3 (23.8-38.6)	14/1.1	12.5 (7.4-21)	5.9 (3.3-10.4)
Age at diagnosis, years										
<1	379	4582.4	17/1.2	14.3 (8.9-23.0)	34.5 (21.6-58.3)	8	17.5 (8.7-34.9)	4/0.2	24.1 (9.0-64.1)	8.4 (3.1-23.3)
1-4	1405	17988.8	89/5.8	15.4 (12.5-18.9)	46.3 (37.8-58.5)	60	33.4 (25.9-43)	14/0.7	19.3 (11.4-32.6)	7.4 (4.3-12.9)
5-9	1076	13802.3	75/6.7	11.2 (8.9-14.0)	49.5 (39.2-64.0)	50	36.4 (27.6-48.1)	8/0.8	10.4 (5.2-20.9)	5.3 (2.3-11.2)
10-14	1103	13330.4	65/8.6	7.5 (5.9-9.6)	42.3 (31.3-55.2)	35	26.5 (19.0-36.9)	6/1.1	5.5 (2.5-12.1)	3.7 (1.0-9.8)
Treatment era										
1976 - 1983	577	13970.7	98/9.4	10.4 (8.6-12.7)	63.4 (51.3-79.3)	57	41.1 (31.7-53.3)	15/1.2	12.2 (7.4-20.3)	9.9 (5.7-17.2)
1984 - 1991	901	17017.5	61/7.8	7.8 (6.1-10.0)	31.2 (24.2-42.4)	31	18.2 (12.8-25.9)	9/0.9	10.1 (5.2-19.4)	4.8 (2.3-9.8)
1992 - 1999	1182	13624.2	58/4.1	14.1 (10.9-18.2)	39.5 (30.7-52.9)	44	32.4 (24.1-43.5)	5/0.5	10.2 (4.3-24.6)	3.3 (1.3-8.8)
2000 - 2007	1305	5091.5	29/1.0	28.7 (19.9-41.3)	55.0 (37.8-80.2)	21	41.3 (26.9-63.4)	3/0.2	19.3 (6.2-59.9)	5.6 (1.7-18.4)
Recurrence										
No	3496	44475.6	134/19.8	6.8 (5.7-8.0)	25.4 (20.8-31.0)	66	14.9 (11.7-19)	24/2.5	9.8 (6.5-14.6)	4.7 (3.0-7.5)
Yes	469	5228.3	112/2.6	43.7 (36.3-52.6)	210.9 (174.7-254.5)	86	165.2 (133.8-204.1)	8/0.3	26.5 (13.3-53.0)	14.9 (7.3-30.4)
Radiotherapy										
No	2411	28367.2	74/10.9	6.8 (5.4-8.5)	22.3 (17.1-29.1)	48	17.0 (12.8-22.5)	4/1.4	3.0 (1.1-7.9)	0.9 (0.2-4.1)
Yes	1251	17590.6	159/9.5	16.8 (14.4-19.6)	86.1 (73.1-101.3)	99	56.4 (46.4-68.7)	26/1.2	22.4 (15.3-32.9)	14.2 (9.4-21.1)
Unknown	303	3474.1	13/1.9	6.7 (3.9-11.6)	30.2 (16.2-56.2)	6	16.1 (7.2-35.9)	2/0.3	8.0 (2.0-31.8)	5.1 (1.2-22.0)
Chemotherapy										
No	733	8560.5	15/3.6	4.2 (2.5-6.9)	14.2 (7.7-26.3)	9	10.5 (5.5-20.3)	0/0.5	NA	NA
Yes	2981	37644.3	218/16.9	12.9 (11.3-14.8)	53.7 (46.6-62.0)	138	36.8 (31.1-43.5)	30/2.1	14.5 (10.2-20.8)	7.4 (5.0-10.8)
Unknown	251	3499.1	13/1.9	6.9 (4.0-12.0)	32.6 (17.6-60.4)	6	17.3 (7.8-38.4)	2/0.2	8.2 (2.1-32.9)	5.5 (1.3-23.6)
Transplantation										
No	3467	44119.1	194/19.6	9.9 (8.6-11.4)	39.8 (34.1-46.5)	123	28.0 (23.4-33.4)	20/2.4	8.3 (5.3-12.8)	3.9 (2.3-6.4)
Allogeneic	94	938.0	20/0.4	48.5 (31.3-75.2)	208.9 (133.5-326.7)	9	98.2 (51.1-188.7)	7/0	147.8 (70.5-310.1)	75.8 (36.0-159.9)
Autologous	74	617.7	16/0.2	65.6 (40.2-107.1)	256.4 (156.3-420.6)	13	210.5 (122.2-362.4)	2/0	72.8 (18.2-291.1)	31.9 (7.8-130.3)
Unknown	330	4029.2	16/2.1	7.6 (4.7-12.4)	34.4 (19.6-60.4)	7	17.5 (8.3-36.7)	3/0.3	10.9 (3.5-34.0)	7.1 (2.2-23.5)

Table 1. Life status, standardized mortality ratios (SMR) and absolute excess risks (AER) for 5-year survivors of childhood cancer diagnosed at age 0–14 years between 1976 and 2007 (SMR and AER are standardized according to age-, sex-, and calendar year) (Continued)

	Eligible Cohort	All causes of death				Recurrent/progressive disease[1]		2nd cancer[1]		
		PY	Obs/Exp	SMR	AER[2]	Obs	Crude rate[3]	Obs/Exp	SMR	AER[2]
Years from cancer diagnosis, years										
5-14	3965	30247.2	199/10.9	18.3 (15.9-21.0)	62.2 (53.9-72.2)	139	46.1 (39.1-54.5)	21/1.2	18.2 (11.8-27.9)	6.6 (4.2-10.4)
15-24	2203	15034.2	30/8.4	3.6 (2.5-5.1)	14.4 (8.4-23.1)	10	6.7 (3.6-12.4)	8/0.9	8.6 (4.3-17.1)	4.7 (2.0-10.2)
≥ 25	882	4422.5	17/3.1	5.6 (3.5-8.9)	31.5 (15-53.8)	4	9.1 (1.1-2750.6)	3/0.7	4.5 (1.4-13.9)	5.3 (0.8-24.7)
Attained age, years										
0-19	1462	7232.7	174/1.1	161.8 (139.5-187.8)	239.1 (204.5-276.2)	124	172.1 (144.3-205.2)	21/0.2	97.2 (63.4-149.0)	28.8 (18.7-44.4)
20-29	1390	17184.5	48/5.6	8.6 (6.5-11.4)	24.7 (14.0-30.9)	24	14.0 (9.4-20.9)	5/0.6	8.2 (3.4-19.7)	2.6 (0.7-7.0)
30-39	856	18303.8	13/9.6	1.4 (0.8-2.3)	1.9 (0.0-34.1)	2	1.1 (0.3-4.4)	4/1.1	3.7 (1.4-9.9)	1.6 (0.1-9.3)
40-49	254	6889.6	11/6.0	1.8 (1.0-3.3)	7.3 (0.7-32.9)	3	4.4 (1.4-13.6)	2/0.8	2.4 (0.6-9.5)	1.7 (0.0-110.2)
≥50	3	93.4	0/0.1	NA	NA	0	NA	0/0.0	NA	NA
Childhood cancer diagnosis[4]										
I. Leukaemia	1289	16464.3	106/7.0	15.1 (12.5-18.2)	60.1 (49.2-73.8)	68	41.5 (32.7-52.7)	16/0.9	18.6 (11.4-30.4)	9.2 (5.4-15.4)
Ia. ALL	576	14908.2	86/6.4	13.4 (10.9-16.6)	53.7 (42.8-67.4)					
Ib. AML	679	1222.1	14/0.5	28.2 (16.7-47.5)	109.7 (63.5-189.5)					
II. Lymphoma	576	7893.8	25/5.0	5.0 (3.4-7.4)	25.3 (14.3-40.0)	8	10.2 (5.1-20.4)	5/0.6	8.3 (3.5-20.0)	5.6 (1.7-15.1)
IIa. Hodgkin lymphoma	237	3251.6	16/2.2	7.3 (4.5-11.9)	39.8 (21.8-72.8)					
IIb. Non-Hodgkin lymphoma	191	2640.6	8/1.7	4.7 (2.3-9.3)	25.0 (10.9-57.7)					
III. CNS tumours	679	692.5	51/3.3	15.7 (11.9-20.6)	63.9 (48.6-86.5)	41	54.9 (40.4-74.6)	3/0.4	7.4 (2.4-23.0)	3.5 (1.1-12.6)
IIIa. Ependymoma	62	692.5	11/0.3	36.8 (20.4-66.5)	155.7 (85.3-284.5)					
IIIb. Astrocytoma	294	3104.6	15/1.2	12.5 (7.5-20.7)	45.9 (27.0-78.2)					
IIIc. PNET	22	205.0	1/0.1	15.3 (2.2-108.4)	44.5 (5.2-381.9)					
IIIc. Medulloblastoma	109	1319.1	17/0.7	25.9 (16.1-41.7)	123.5 (75.2-202.7)					
IV. Neuroblastoma	218	2749.4	15/0.8	18.9 (11.4-31.3)	51.7 (31.2-88.9)	10	36.4 (19.6-67.6)	1/0.1	9.5 (1.3-67.2)	3.3 (0.4-28.5)
V. Retinoblastoma	131	1733.1	4/0.5	8.3 (3.1-22.1)	20.3 (6.3-61.7)	0	NA	3/0.1	47.2 (15.2-146.5)	16.9 (5.3-53.9)
VI. Renal tumours	235	3056.4	6/0.9	6.8 (3.1-15.2)	16.8 (7.5-43.1)	3	9.8 (3.2-30.5)	2/0.1	16.6 (4.2-66.4)	6.2 (1.5-26.7)
VII. Hepatic tumour	28	328.2	1/0.1	9.0 (1.3-63.6)	27.1 (3.9-224.2)	1	30.5 (4.3-216.3)	0/0.0	NA	NA
VIII. Bone tumours	159	1863.2	15/1.1	14.2 (8.6-23.6)	74.8 (43.4-128.9)	10	54.8 (29.5-101.9)	1/0.1	7.8 (1.1-55.3)	4.8 (0.5-46.9)
VIIIa. Osteosarcoma	74	888.8	5/0.5	9.1 (3.8-22.0)	51.0 (19.5-133.9)					
VIIIc. Ewing sarcoma	77	796.5	10/0.4	25.8 (13.9-47.9)	119.5 (62.4-229.1)					

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	Eligible Cohort	All causes of death				Recurrent/progressive disease[1]		2nd cancer[1]		
		PY	Obs/Exp	SMR	AER[2]	Obs	Crude rate[3]	Obs/Exp	SMR	AER[2]
IX. Soft-tissue sarcomas	244	3130.0	16/1.5	10.3 (6.3-16.9)	46.2 (27.7-80.0)	10	32.0 (17.2-59.4)	1/0.2	5.3 (0.7-37.4)	2.6 (0.3-25.2)
IXa. Rhabdomyosarcoma	137	1750.7	7/0.8	8.9 (4.2-18.6)	35.7 (15.6-81.5)					
IXd. Other soft-tissue sarcomas	105	1325.7	9/0.7	12.8 (6.7-24.6)	64.1 (32.1-127.9)					
X. Germ cell tumours	119	1548.0	1/0.6	1.6 (0.2-11.1)	2.3 (0.3-70.0)	1	6.5 (0.9-45.9)	0/0.1	NA	NA
Other cancers	287	3467.8	6/1.5	3.9 (1.8-8.7)	12.9 (5.1-37.2)	1	2.9 (0.4-20.5)	0/0.2	NA	NA

[1]Subjects with unknown causes of death were *a priori* excluded.
[2]Per 10'000 person-years at risk.
[3]Can be interpreted as an absolute excess risk.
[4]According to the International Classification of Childhood Cancer, 3rd edition.
Abbreviations: PY: person-years; Obs: observed; Exp: expected; CI: confidence interval; NA: not applicable; ALL: acute lymphoblastic leukaemia; AML: acute myeloid leukaemia; CNS: central nervous system; PNET: primitive neuroectodermal tumours

function of time since diagnosis for different causes of death and different diagnostic periods. We used logrank test for trend to test for trends in CM and treated causes of death, other than the one under observation, as competing risks using the "stcompet" command in STATA. Between 1976 and 1981, the SCCR mainly registered children who were included in clinical studies. We assume that certain tumors, especially those not treated in a specialized pediatric cancer center, were not registered in the SCCR. In a sensitivity analysis, we repeated our main analysis of overall SMR considering only cases diagnosed 1985–2007. *p*-values were two sided; we considered a p values of ≤ 0.05 to be statistically significant. STATA, version 13 was used for all statistical analyses (StataCorp. 2013. Stata Statistical Software: Release 13.1.College Station, TX: StataCorp LP).

Results

Cohort characteristics

Of 5,190 children diagnosed with cancer in Switzerland between 1976 and 2007, 3,965 (76%) were long-term survivors for 5 years or more. By the study exit date, 246 (6.2%) of them had died, 113 (2.9%) were lost-to-follow-up, and 3,606 (91.0%) were still alive. COD was available for 226 (92.0%) of the deceased. In 23 of 226 cases (10.2%), handwritten information on the death certificate or the patients' medical history caused us to recode the official COD from primary cancer to a second cancer ($N = 13$), or a non-cancer late fatality ($n = 10$). We included 49'704 person-years at risk from 5-year survival. Mean follow-up time was 17.5 (95% confidence interval [CI] 17.3–17.8) years from diagnosis; median was 16.5 years (range 5.0 to 36.9). Information on radiotherapy was missing for 303 patients (7.6%), on chemotherapy for 251 patients (7.6%), and on HSCT for 330 patients (8.3%).

Overall mortality

Survivors were 11 times more likely to die than their peers in the general population (SMR 11.0). There were 45 extra deaths (AER 45.0) per 10,000 person-years (Table 1). SMR was higher in females (SMR 18.4) than males (SMR 8.5), while the AER was comparable. The SMR was higher in children diagnosed at ages <1 year (SMR 14.3) and 1–4 years (SMR 15.4) than in those diagnosed at ages 5–9 (SMR 11.2) and 10–14 (SMR 7.5). Those who had had recurrent disease within 5 years of diagnosis were likely to have considerably higher mortality from any cause (SMR 43.7) than those without recurrence during that period (SMR 6.8). Children who had autologous (SMR 65.6) or allogeneic HSCT (SMR 48.5) in the first 5 years after diagnosis had significantly higher SMR compared to those without HSCT (SMR 9.9). The SMR declined with increasing follow-up time and attained age ($p < 0.001$ for trend). However, significant excess mortality remained beyond 24 years from diagnosis (SMR 5.6). Number of excess deaths was largest during the first 10 years after

Table 2. Observed and expected numbers of death, standardized mortality ratio (SMR) and absolute excess risk (AER) for specific causes of death

	Obs/Exp	SMR (95% CI)	AER[1] (95% CI)
All causes of death	226/22.2	10.2 (8.9-11.6)	41.2 (36.1-48)
Recurrent/progressive disease	153/0.0	NA	30.9 (26.4-36.2)
All causes except recurrence	73/22.2	3.3 (2.6-4.1)	10.3 (7.2-13.8)
2nd cancer	32/2.8	11.6 (8.2-16.4)	5.9 (4.0-8.5)
All causes except cancer	41/19.5	2.1 (1.6-2.9)	4.3 (2.1-7.2)
Diseases of the circulatory system	16/1.3	12.7 (7.8-20.7)	2.9 (1.5-4.7)
Diseases of the respiratory system	4/0.3	14.8 (5.6-39.4)	0.7 (0.3-2.2)
Infectious diseases	4/0.5	7.3 (2.7-19.4)	0.7 (0.2-2.2)
External causes	13/12.8	1 (0.6-1.8)	0.0 (0.0-7.4)
Other causes[2]	4/4.6	0.9 (0.3-2.3)	NA

[1]Per 10'000 person-years at risk.
[2]All other causes of death other than the ones aforementioned.
Abbreviations: Obs: observed; Exp: expected; CI: confidence interval.

5-year survival (AER 62.2), declined thereafter between 15 and 24 years after diagnosis (AER 14.4) and increased again beyond 24 years after diagnosis (AER 31.5). We observed the greatest SMRs among survivors of ependymoma (SMR 36.8), AML (SMR 28.2), medulloblastoma (SMR 25.9) and Ewing sarcoma (25.8). AER varied widely by primary cancer diagnosis and was largest for those diagnosed with ependymoma (AER 155.7), Ewing sarcoma (AER 119.5) and AML (AER 109.7). In regard of ICCC-3 main group, the SMR was highest for children diagnosed with neuroblastoma (SMR 18.9), CNS tumours (SMR 15.7), leukaemia (SMR 15.1) and bone tumours (SMR 14.2). AER was largest for bone tumours (AER 74.8), CNS tumours (AER 63.9), leukaemia (AER 60.1) and neuroblastoma (AER 51.7).

Cause-specific mortality

SMRs were significantly elevated for deaths from second cancers (SMR 11.6), diseases of the circulatory system (SMR 12.7), diseases of the respiratory system (SMR 14.8) and infectious diseases (SMR 7.3) (Table 2). Mortality was not increased for deaths due to other medical causes (SMR 0.9) and external causes (SMR 1.0). Highest number of excess deaths was observed for deaths due to recurrence or progression of the original cancer (AER 30.9), second cancer (AER 5.9) and circulatory disease (AER 2.9). For diseases of the respiratory system, and infectious diseases, AERs were <1 per 10'000 person-years.

We then proceeded to determine potential explanatory factors for all cause mortality, recurrence, second cancers and circulatory diseases. To do this, we stratified SMR and AER by different explanatory factors. Crude mortality rate for recurrence or progression of the original cancer, which can be interpreted as an AER, was highest in survivors of CNS tumours (AER 54.9) and bone tumours (AER 54.8) (Table 1). Number of excess deaths due to recurrence was highest at 5 to 14 years from diagnosis (AER 46.1) and declined to below 10 excess deaths beyond 14 years from diagnosis. Multivariable analysis showed that children who suffered from recurrent disease during the first 5 years after diagnosis were at higher risk of death due to recurrence or progression (RR 8.2) than those without recurrence (Table 3). Children treated with radiotherapy (RR 2.2), chemo therapy (RR 4.4), or autologous HSCT (RR 3.7) in the first 5 years after diagnosis were more likely to die from recurrence than those who did not receive radiotherapy, chemotherapy or HSCT.

SMR for second cancers was highest for children originally diagnosed with retinoblastoma (SMR 47.2) and leukaemia (SMR 18.6) (Table 1). Mortality due to second cancers was relatively stable over follow-up time with 6.6 excess deaths at 5–14 years after diagnosis, 4.7 at 15–24 years and 5.3 excess deaths beyond 24 years from diagnosis. Multivariable analysis showed that children treated with radiotherapy (RR 9.2), allogeneic HSCT (RR 12.5) or autologous HSCT (RR 6.3) had a higher risk for death due to second primary cancer than those without radiotherapy or HSCT (Table 3). Those who had had recurrent disease within the first 5 years after diagnosis had the same risk for mortality due to second cancers as those who did not have recurrence.

From 5–14 years after diagnosis, recurrence accounted for 78.9% of all excess deaths, second cancers for 11.3%, circulatory diseases for 4.9% and all other causes of death for 2.9% (Table 4). Beyond 24 years after diagnosis the proportion decreased to 36.5% for recurrence, but increased to 21.3% for second cancers, to 33.3% for circulatory diseases and to 8.9% for all other causes of death.

Cumulative mortality

Cumulative mortality (CM), which can be interpreted as a probability of death, was 8.8% (CI 6.4–15.0) at 30 years after diagnosis for all 5-year survivors (Fig. 1). The CM for death from recurrence or progression increased steeply with time from diagnosis, to 3.3% (CI 2.8-4.0) at 10 years. It then

Table 3. Risk ratios for death from different causes of death and 95% confidence intervals for different explanatory factors (adjusted for all variables shown)

	All causes of death		Recurrent/progressive disease		Second cancer	
	Risk ratio (95% CI)	p[1]	Risk ratio (95% CI)	p[1]	Risk ratio (95% CI)	P[1]
Sex		0.800		0.895		0.919
Male	1		1		1	
Female	1.04 (0.78-1.38)		1.02 (0.74-1.42)		1.04 (0.48-2.26)	
Age at diagnosis, years		0.958		0.974		0.285
<1	1.14 (0.63-2.09)		0.85 (0.39-1.87)		2.36 (0.57-9.79)	
1-4	1		1		1	
5-9	0.97 (0.69-1.37)		1.05 (0.71-1.55)		0.55 (0.2-1.49)	
10-14	1.09 (0.73-1.62)		1.1 (0.7-1.73)		0.36 (0.1-1.26)	
Treatment era		<0.001		0.001		0.287
1976 - 1983	1		1		1	
1984 - 1991	0.55 (0.37-0.8)		0.44 (0.28-0.7)		0.72 (0.27-1.95)	
1992 - 1999	0.47 (0.32-0.68)		0.48 (0.31-0.74)		0.34 (0.11-1.07)	
2000 - 2007	0.55 (0.34-0.89)		0.5 (0.29-0.86)		0.63 (0.16-2.54)	
Childhood cancer diagnosis[2]		<0.001		<0.001		0.851
I Leukaemia	1		1		1	
II Lymphoma	0.32 (0.16-0.65)		0.27 (0.13-0.58)		0.77 (0.18-3.17)	
III CNS tumours	1.96 (1.28-3.0)		2.29 (1.44-3.65)		1.16 (0.28-4.8)	
IV Neuroblastoma	1.12 (0.59-2.14)		1.14 (0.53-2.44)		0.39 (0.04-3.77)	
V Retinoblastoma	0.52 (0.15-1.81)		NA		1.73 (0.33-9.02)	
VI Renal tumours	0.42 (0.17-1.07)		0.35 (0.11-1.13)		1.04 (0.21-5.2)	
VII Hepatic tumour	1.15 (0.15-8.69)		1.76 (0.23-13.33)		NA	
VIII Bone tumours	1.56 (0.82-2.98)		1.67 (0.82-3.38)		1.56 (0.17-14.58)	
IX Soft-tissue sarcomas	1.03 (0.57-1.88)		1.07 (0.53-2.13)		0.51 (0.06-4.33)	
X Germ cell tumours	0.14 (0.02-1.19)		0.22 (0.03-1.65)		NA	
Other cancers	0.55 (0.21-1.44)		0.15 (0.02-1.1)		NA	

Table 3. Risk ratios for death from different causes of death and 95% confidence intervals for different explanatory factors (adjusted for all variables shown) (Continued)

	All causes of death		Recurrent/progressive disease		Second cancer	
	Risk ratio (95% CI)	p[1]	Risk ratio (95% CI)	p[1]	Risk ratio (95% CI)	P[1]
Recurrence		<0.001		<0.001		0.682
No	1		1		1	
Yes	6.05 (4.47-8.21)		8.19 (5.81-11.55)		0.81 (0.3-2.22)	
Radiotherapy		<0.001		0.005		0.002
No	1				1	
Yes	2.22 (1.58-3.13)		1.84 (1.26-2.68)		9.24 (2.58-33.15)	
Unknown	0.5 (0.03-8.32)		0.57 (0.01-30.35)		0.53 (0-1284.82)	
Chemotherapy		<0.001		<0.001		0.093
No	1		1		1	
Yes	4.42 (2.11-9.28)		4.3 (2.04-9.06)		NA	
Unknown	11.19 (0.62-201.74)		13.35 (0.23-791.31)		NA	
HSCT		0.001		0.001		<0.001
No	1		1		1	
Allogeneic	1.43 (0.84-2.44)		0.86 (0.42-1.78)		12.52 (3.8-41.18)	
Autologous	3.68 (2.07-6.55)		4.21 (2.22-8)		6.29 (1.25-31.71)	
Unknown	1.04 (0.35-3.08)		0.56 (0.12-2.68)		3.62 (0.44-29.52)	
Years after diagnosis		<0.001		<0.001		0.218
5-9	1		1		1	
15-24	0.2 (0.12-0.34)		0.14 (0.07-0.27)		0.57 (0.23-1.44)	
>24	0.18 (0.07-0.49)		0.12 (0.04-0.34)		0.27 (0.03-2.88)	

[1]*p* values from likelihood ratio test.
[2]According to the International Classification of Childhood Cancer, 3rd edition.
Abbreviations: CI: confidence interval; NA: not applicable; CNS: central nervous system.

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Table 4. Absolute excess risks (AER) by years from diagnosis as a proportion of total AER

	AER (%[1]) by years from diagnosis		
Cause of death	**5-14**	**15-24**	**>24**
Recurrent/progressive disease	46.1 (78.9)	6.7 (51.0)	9.1 (36.5)
Second cancer	6.6 (11.3)	4.7 (36.0)	5.3 (21.3)
Circulatory disease	2.8 (4.9)	1.7 (12.8)	8.3 (33.3)
Other causes of death	2.9 (5)	NA	2.2 (8.9)
All deaths[2]	58.4	13.1	24.9

[1]Proportion of total AER during specific time period since diagnosis.
[2]Number of AER differs slightly from number indicated in Table 1 due to unknown cause of death in 20 patients.

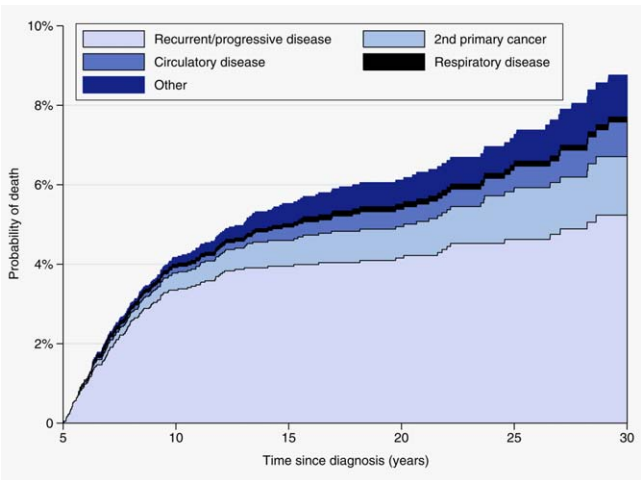

Figure 1. Cause-specific probability of death for different causes of death in 5-year survivors of childhood cancer diagnosed at age 0–14 years between 1976 and 2007 (cumulative mortality treating cause of death other than the one under observation as competing risks).

increased at a slower pace, to 5.2% (CI 4.3-6.3) at 30 years from diagnosis. The CM for all causes except recurrence was 10.8% (CI 0.6-1.2) at 10 years from diagnosis, but increased continuously to 3.5% (CI 2.6–4.6) at 30 years from diagnosis.

CM decreased significantly with time of diagnosis for 5-year survivors of childhood cancer (Fig. 2). The probability of dying from all causes of death combined within the next 5 years dropped most markedly between the periods 1976–1983 (9.0%, CI 6.9–11.6) and 1984–1993 (3.9%, CI 1.7–3.8). CM at 10 years after diagnosis did not differ significantly between later periods due to low numbers. But we observed an on-going trend for decreasing CM when looking at the total follow-up time of all 4 periods (p-trend < 0.001).

Sensitivity analysis

We further performed a sensitivity analysis by considering only cases diagnosed since 1985. Results did not materially change: the overall SMR was 11.4 (CI 9.7–13.4) and the AER 38.6 (CI 32.5–45.9).

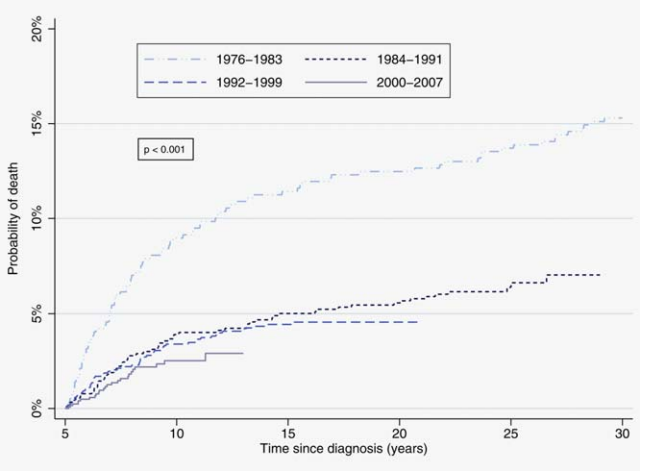

Figure 2. Cumulative mortality from all causes in 5-year survivors of childhood cancer diagnosed at age 0–14 years according to the specific treatment area. p values form log-rank test for trend.

Discussion

This population-based cohort of 5-year survivors of childhood cancer showed that this group of patients remains at significantly increased risk for death 30 years after diagnosis. At 5–14 years after diagnosis, 79% of all extra deaths were caused by recurrence of the primary cancer, but this proportion decreased to 37% $\geq$24 years from diagnosis. In contrast, the proportion of extra deaths from second cancers, circulatory diseases, respiratory diseases and other diseases increased steadily with time from diagnosis and accounted for 64% of all deaths occurring beyond 24 from diagnosis. Cumulative mortality beyond 5 years after diagnosis decreased significantly over time.

The SMR estimated in our study was consistent with results from the British Childhood Cancer Survivor study (BCCSS) (SMR 10.7), and was somewhat higher than had been reported from the Childhood Cancer Survivor study (CCSS) (SMR 8.4) and the Nordic countries (SMR 8.3).[10,11,20] A study from Scotland, similar in size to our own, analysed long-term cause-specific mortality among children, adolescents and young adults with cancer; this study reported an overall SMR for childhood cancer (age at diagnosis 0–14 years) of 11.0 similar to ours, but found a slightly higher number of AER (51).[12] Similar to our study, the CCSS reported highest SMRs among survivors of Ewing sarcomas and medulloblastomas or PNET. However, the CCSS did not differentiate between PNET and medulloblastomsa.[20] In contrast the CCSS found a lower SMR for AML (SMR 9.5) compared to our study. In terms of ICCC-3 main groups, the high overall SMR for leukaemia and CNS tumours (SMR $>$ 15) estimated in our study were comparable to findings from other studies.[11,12,20] However, most other studies reported a lower overall SMR for neuroblastomas. In our study, SMR for deaths due to diseases of the respiratory system, circulatory system and second cancer was largest (SMR $>$ 10). This was slightly higher than reported in the

BCCSS (for all three causes of death) and in the Nordic study (for circulatory diseases and second cancers).[11,24] Similar to our study SMR was highest for diseases of the respiratory system (SMR 34.9) as reported in a study from the Nordic countries.[10] In our study, mortality from external causes (including suicide) was not elevated, in contrast to the BCCSS.[11] It is important to note, that there is some heterogeneity regarding age at diagnosis of the primary cancer, calendar period of diagnosis and length of follow-up in comparing studies. The decrease of AER for deaths due to recurrence and simultaneous increase of AER to other causes of death over study time was consistent with findings from the BCCSS, although it has a longer period of follow-up.[11] Other studies did not compare cause specific SMR or AER at different times since diagnosis. Crude mortality rates for recurrence deaths estimated in our study were highest for CNS tumours bone tumours and leukaemia. This is comparable to results form the BCCSS, which reported crude rates for recurrence deaths to be highest for PNET, leukaemia (excluding ALL), CNS tumours (excluding PNET) and bone tumours.[11] Most other studies did not report crude rates for deaths due to recurrence for underling cancer diagnosis. Like in our study, the BCCSS reported high SMR for second cancers for children diagnosed with retinoblastoma. However, we were not able to distinguish between heritable and non-heritable retinoblastoma and we assume that the heritable form of the disease drove the high SMR for retinoblastoma rather than treatment related causes. Like our study, studies from United States, United Kingdom and the Nordic countries showed that CM from recurrence increased during the first 10 years from diagnosis, and then levelled off, while CM for second cancers and circulatory diseases, increased continuously with follow-up time. In 2012 Garwicz *et al.* explored temporal trends in CM using data from the Nordic countries.[10] Similar to our study the most marked decrease in CM was observed for patients diagnosed during the 1980 sec compared to those diagnosed during the 1970 sec. However, the decrease in cumulative mortality from the first to the subsequent diagnostic period be interpreted cautiously. As commonly is the case in cancer registration, completeness of the SCCR was somewhat lower in its early years compared to today. Because the SCCR started as a clinical registry and registered mostly children enrolled in clinical studies, we assume that certain cancers were not registered completely, especially low grade CNS tumours and melanomas. The cumulative mortality observed for children diagnosed 1976–1984 may therefore have been overestimated. However, a sensitivity analysis showed that overall estimates of all cause SMR and AER did not change substantially when excluding the first period from the analysis (1976–1984).

Excess mortality due to second cancers, circulatory diseases and diseases of the respiratory system are likely caused by late effects of cancer treatment.[13,34–38] Second cancers are widely accepted as a late effect of radiotherapy during the treatment, but also specific chemotherapeutic agents might be involved in the development of second cancers. Some second cancers might also be attributable to familial cancer syndromes like heritable retinoblastoma and Li–Fraumeni syndrome.[39–41] Thus, the elevated SMR for second cancers in children diagnosed with retinoblastoma is a combination of treatment related late toxicities and genetic predisposition. Circulatory diseases may also be a late complication of childhood cancer therapy, primarily related to chest radiation or anthracyclines. Similar to the BCCSS and the CCSS cohort, we have also demonstrated adverse respiratory late effects among childhood cancer survivors. However, this should be interpreted cautiously in the context of this rare disease with only 4 (1.8%) out of 226 late deaths attributable to it.

One of the main advantages of this study was the combination of three resources. First, information on original childhood cancer diagnosis came from the population-based SCCR. The SCCR is very complete (>95% since 1995) and its not susceptible to response bias compared to questionnaire-based studies. Second, clinical data such as information on treatment and follow-up was reported directly from the nine specialized paediatric oncology clinics throughout Switzerland. We had access to most medical records and could validate treatment and follow-up data. Third, we had access to official death certificates and were able to validate code causes of death from official mortality statistics. This is important since it has been shown that deaths attributable to recurrence of the primary cancer can be overestimated, and consecutive or contributing causes of death (which might reflect therapy induced late effects) can be underestimated.[24,42] Another advantage of our study was that we were able to include recently diagnosed patients (up to 2007), which many other studies could not do.[11,18,20] But, our study was smaller than other studies, so we had limited capacity to perform subgroup analyses. Another limitation of our study was the lack of detailed data on radiotherapy and chemotherapy exposures and lack of data on applied dosages. Therefore, we were no able to analyse the effect of dose-response patterns on risk of morality. We validated COD of childhood cancer survivors, since cancer deaths were most probably overestimated. We must assume that this was also true for cancer deaths in the official statistics. If true, this would have led to an overestimation of expected deaths due to (second) cancer in our analysis and thus to an underestimation of second cancer specific SMR. The form of the death certificate changed over the study period. However, data items concerning causes of death remained unchanged. Further, there has been a change in the coding system in the mortality statistics in Switzerland from ICD-8 to ICD-10 and an adaption of coding rules, which could introduce breaks into time series of disease coding. However, since we classified COD into broad categories, we assume that this break in the coding system and rules did not affect the results of our study. Deaths due to late effects of the treatment may have declined over time due to better follow-up care. If late effects become less fatal, mortality may become a less reliable

indicator of the incidence of these late effects. This suggests that future studies should also address morbidity, not only mortality.

Clinicians and patients need information on long-term outcomes, and especially mortality, to make sound decisions about treatment and follow-up. We demonstrated the usefulness of linking baseline cancer registry data and clinical data on treatment to routinely collected mortality records to monitor fatal late-effects inexpensively. Our results underline the importance of follow-up programs lasting years after the end of treatment for childhood cancer, and we suggest the use of standardized risk-adapted protocols for monitoring health conditions in the growing population of childhood cancer survivors. In absolute numbers, second cancers and circulatory disease account for most excess deaths in survivors diagnosed over 24 years ago, but this population is also less likely to attend follow-up than those were more recently diagnosed.[43] Our results underline the importance of follow-up programs lasting years after the end of treatment for childhood cancer, and we suggest a standardized protocol would be useful for detailed monitoring of health conditions in detail in the growing population of childhood cancer survivors.

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