swiss childhood cancer registry

annual report 2013-2014

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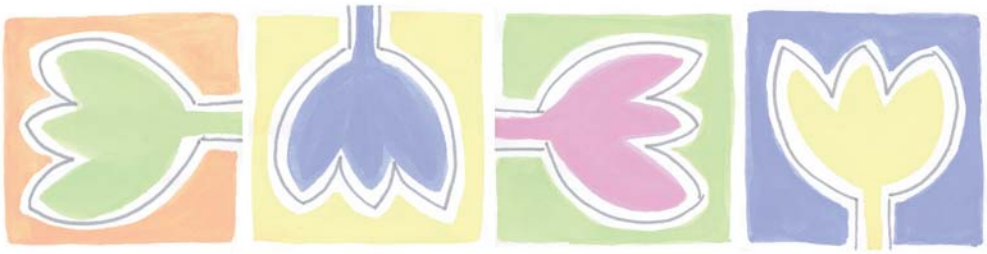
Swiss Childhood Cancer Registry
Annual Report 2013/2014



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Bern, Swiss Childhood Cancer Registry

Table of contents

1. Introduction **7**

2. Organisation of the Swiss Childhood Cancer Registry **9**

2.1 Institute of Social and Preventive Medicine (ISPM), University of Bern 9
2.2 Swiss Paediatric Oncology Group (SPOG) 10
2.3 General information 11

3. Routine Analyses **13**

3.1 Overview 13
3.2 All cases registered in the SCCR (N=8957) 13
3.3 Swiss residents aged 0-14 years at diagnosis (N=6371) 15
3.4 Swiss residents aged 15-20 years at diagnosis (N=450) 21

4. Research projects on childhood cancer **23**

4.1 Swiss Childhood Cancer Survivor Study (SCCSS) 24
4.2 Follow-up Care After Childhood and Young Adult Cancer (CCFU) 25
4.3 PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies (PanCareSurFup) 26
4.4 PanCare Studies in Fertility and Ototoxicity to Improve Quality of Life after Cancer during Childhood, Adolescence and Young Adulthood (PanCareLIFE) 27
4.5 Risk of Cancer and Long-Term Mortality in Children Treated with Growth Hormone: Swiss Participation in the EU FP7 Project (SAGhE) 27
4.6 Mortality and Second Primary Cancers after Cancer in Childhood and Adolescence 28
4.7 Fertility after Chemo- and Radiotherapy in Childhood and Adolescence, FeCt – Multicentre Offspring Study 28
4.8 Parents of Long-Term Childhood Cancer Survivors 29
4.9 Effectiveness of Transition from Paediatric to Adult Care after Childhood Cancer 30
4.10 Childhood Cancer and Vicinity of Residence to Petrol Stations and Roads: Census-Based Nationwide Cohort Study (PETROL) 30
4.11 Childhood Cancer and Geographically Defined Exposures in Switzerland: A Census-Based Nationwide Cohort Study 31
4.12 The Role of Population Mixing and Exposure to Infections in the Aetiology of Childhood Leukaemia: A National Cohort Study 31
4.13 The Spatial Epidemiology of Childhood Cancer in Switzerland 32

5. Publications **33**

5.1 Publications in peer-reviewed journals 33
5.2 Publications in other journals 35
5.3 Publications in lay journals 35
5.4 Reports 36

6. Appendix: Classification of cancer diagnoses **37**

1. Introduction

The Swiss Childhood Cancer Registry (SCCR) is the national population-based cancer registry for children and adolescents in Switzerland. New cancer diagnoses, clinical information, details on treatment and long-term follow-up (survival, second primary neoplasms and late effects) have been registered in the SCCR since 1976. With many associated research projects and through close collaboration with clinicians it contributes to understanding the causes of cancer in children, improving follow-up care and reducing late effects.

The SCCR is located at the Institute of Social and Preventive Medicine (ISPM) at the University of Bern. It is operated jointly by the Swiss Paediatric Oncology Group (SPOG) and the University of Bern. Since 1976, all nine Swiss paediatric haematology-oncology centres report newly diagnosed cases to the registry and send annual updates on clinical follow-up. Since 2007, the SCCR collects supplementary data also from other sources, including cantonal cancer registries, other hospitals, pathology laboratories and the Swiss Federal Statistical Office (SFSO). As of 31st December 2013, data from 8957 cases (diagnosed in 8608 patients) have been registered.

The SCCR is authorized to collect non-anonymised data. The permission has been issued in 2007 by the Federal Commission of Experts for Professional Secrecy in Medical Research (Eidgenössische Expertenkommission für das Berufsgeheimnis in der medizinischen Forschung). Since 2014 the new act on human research is in place; the SCCR got a new authorization issued by the ethics committee of the canton of Bern in July 2014.

The SCCR is an associated member of the National Institute for Cancer Epidemiology and Registration (NICER), of the European Network of Cancer Registries (ENCR) and of the International Association of Cancer Registries (IACR), and collaborates with childhood cancer registries throughout Europe.

This sixth annual report covers the routine analyses of all children diagnosed between 1st January 1976 and 31st December 2013. Activities, projects and publications of the SCCR are described for the years 2013 and 2014. The report contains:

- An overview of the organisation and team of the SCCR, SPOG and the participating paediatric haematology-oncology centres **(Chapter 2)**
- A summary of the data collected in the registry up to 31st December 2013 **(Chapter 3)**
- A list of current research projects of the SCCR **(Chapter 4)**
- A list of publications **(Chapter 5)**

Our website (www.childhoodcancerregistry.ch) contains further information, including past annual reports and scientific publications.

We would like to thank all the children and their families, and all adolescent and adult childhood cancer survivors, for allowing us to collect their data. We also thank the physicians and data managers of the Swiss Paediatric Oncology Group for their excellent collaboration. Our thanks also go to the cantonal cancer registries, the National Institute for Cancer Epidemiology and Registration (NICER), the Swiss Federal Statistical Office (SFSO), the Federal Office of Public Health (FOPH) and the pathology laboratories for their cooperation. Finally, we thank our supporters for their generous contributions.

2. Organisation of the Swiss Childhood Cancer Registry

The Swiss Childhood Cancer Registry (SCCR) is a member of the Swiss Paediatric Oncology Group (SPOG) and is organised as a joint operation of the Institute of Social and Preventive Medicine (ISPM) at the University of Bern and the SPOG.

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2.3 General information

Aims

The Swiss Childhood Cancer Registry collects information on the diagnosis, treatment and follow-up of children and adolescents with cancer in Switzerland and provides data for national and international statistics and research projects.

It aims:

- To collect representative, population-based data on cancer in children and adolescents in Switzerland (cancer incidence, prevalence, time trends, regional distribution and survival rates)
- To document diagnostic evaluations, treatment and participation in clinical trials
- To describe short-term and long-term prognosis (mortality, morbidity and quality of life) after cancer in childhood and adolescence
- To provide a research platform for clinical, epidemiological and basic research

It thus contributes to:

- Research into the aetiology of cancer in children and adolescents.
- Planning of health services
- Continuous improvement of treatment
- Identifying possible late effects of therapy, with the aim to diagnose and treat them early and prevent them in the future

Inclusion criteria

The SCCR registers all children and adolescents aged 0 to 20 years, resident or treated in Switzerland, diagnosed with:

- Acute and chronic leukaemias, including myelodysplastic syndrome
- Lymphomas
- Malignant solid tumours
- Central nervous system tumours (CNS), malignant and benign tumours
- Langerhans cell histiocytosis (LCH)

Since 2014 it also registers children and adolescents diagnosed with:

- Aggressive fibromatosis (ICD-O-3M code 8821/1)
- Benign/mature teratoma (ICD-O-3M code 9080/0)
- Mesoblastic nephroma (ICD-O-3M code 8960/1)
- Severe aplastic anaemia (ICD-10 D61.9)
- Neoplasms of the liver, histologically proven, but no malformations

Children and adolescents who are not Swiss residents but are diagnosed or treated in Switzerland are registered, but they are excluded from analyses of incidence and survival.

Sources of data

Data on children and adolescents with cancer are collected from several sources, including:

- The nine Swiss centres for paediatric oncology and haematology (**Chapter 2.2**)
- Other hospitals
- Cantonal cancer registries, represented by the National Institute for Cancer Epidemiology and Registration (NICER)
- Clinical and epidemiological registries (e.g. brain tumour registry, bone tumour registry, Swiss growth registry etc.)
- The Swiss Federal Statistical Office (SFSO; Swiss mortality statistics)
- Pathology laboratories

Most children are reported by one of the nine Swiss centres for paediatric oncology and haematology. Local data managers complete forms for all newly diagnosed patients. Basic information on diagnosis is later completed with information on treatments, remissions, relapses, transplantations and health outcomes. These forms are sent to the SCCR and information is entered into the database. Important medical documents (e.g. pathology reports) are scanned and stored electronically using a pseudonym. Paper copies are destroyed. Information on Swiss residency is validated through municipal population registers.

For the first five to ten years after diagnosis follow-up data is extracted annually from patients' hospital records by the local data managers in all paediatric oncology and haematology centres (page 13, **Chapter 3.2**). To assess outcomes after the children have left the clinic, patients are contacted directly with a questionnaire (page 24, **Chapter 4.1**: Swiss Childhood Cancer Survivor Study) and data is linked to mortality records (SFSO) and to records from cantonal cancer registries (page 28, **Chapter 4.6**: Mortality and second primary cancers after cancer in childhood and adolescence). Life status update is assessed through community registries. For children not treated in a paediatric oncology and haematology centre, clinical follow-up from hospitals is often not available, but long-term epidemiological follow-up is done via questionnaires and by assessment of second primary neoplasms and mortality as for the other patients and life status update via community registries (page 13, **Chapter 3.2**).

Clinical database

The current SCCR database was set up in 2007. The following information is routinely collected:

- Tumour diagnosis, date of diagnosis, morphology, topography, stage, metastases
- Other diagnoses (relevant pre-existing conditions)
- Relevant laboratory and clinical data

- Treatment (clinical trial participation, chemotherapy, radiotherapy, surgical intervention, bone marrow transplantation) and treatment centres involved
- Follow-up data (changes of treatment, remissions, relapses, survival/death and cause of death)
- Late adverse outcomes (e.g. cardiovascular diseases, second primary neoplasms and endocrine disorders)

Trust centre

Since 2010, personal information (name and address) is stored in a separate database in the trust centre. The trust centre validates addresses, residence status, nationality, and vital status via community registers. This personal information is separated strictly from clinical information of the SCCR database. The following data is collected:

- Patient name, address of residence at time of diagnosis, current address of residence
- Date of birth, sex, first language
- Country of residence and nationality at time of diagnosis
- Vital status and date of death
- Parental profession, parental date of birth

Tumour coding

All tumours are coded according to the following international classification systems (see appendix):

- International Classification of Childhood Cancer, third edition (ICCC-3)
- International Classification of Diseases for Oncology, third edition (ICD-O-3)
- International Classification of Diseases and Related Health Problems, tenth revision (ICD-10)

In the annual report, the main diagnostic groups of the ICCC-3 are used:

I. Leukaemias, myeloproliferative diseases, and myelodysplastic diseases
II. Lymphomas and reticuloendothelial neoplasms
III. CNS and miscellaneous intracranial and intraspinal neoplasms
IV. Neuroblastoma and other peripheral nervous cell tumours
V. Retinoblastoma
VI. Renal tumours
VII. Hepatic tumours
VIII. Malignant bone tumours
IX. Soft tissue and other extraosseous sarcomas
X. Germ cell tumours, trophoblastic tumours, and neoplasms of gonads
XI. Other malignant epithelial neoplasms and malignant melanomas
XII. Other specified and unspecified malignant neoplasms

Langerhans cell histiocytosis (LCH), which is not included in ICCC-3, is reported separately.

Data protection

In 2004, the SCCR received a special authorisation (Sonderbewilligung) from the Swiss Federal Commission of Experts for Professional Secrecy in Medical Research. Starting from June 2007, a general authorization (Registerbewilligung) permitted the collection data from paediatric cancer patients (children and adolescents) throughout Switzerland after obtaining written, oral or silent consent.

Since January 2014 the new Human Research Act and its three ordinances are in place. Out of those three ordinances the ordinance on Human Research with the exception of Clinical Trials provides the new framework for the SCCR. Instead of the Swiss Federal Commission of Experts for Professional Secrecy in Medical Research, data collection and storage by SCCR now require an authorisation by the ethics committee of the canton of Bern. The general authorization (Registerbewilligung) has been replaced in July 2014 by an approval from the ethics committee of the canton of Bern.

Funding

The SCCR thanks the following supporters for their financial contributions towards the daily operation and the continuous development of the registry. Supporters of scientific research projects are listed in **Table 7** (page 23).

Main funding sources 2013/2014

- Schweizerische Konferenz der kantonalen Gesundheitsdirektoren und -direktorinnen (GDK)
- Schweizerische Pädiatrische Onkologie Gruppe (SPOG)
- Krebsforschung Schweiz
- Kinderkrebshilfe Schweiz
- Stiftung für krebskranke Kinder Regio Basiliensis (2013)
- Ernst Göhner Stiftung
- Interpharma
- AXA-Winterthur

Other funding sources 2013/2014

- National Institute for Cancer Epidemiology and Registration (NICER)
- Novartis
- CSL Behring
- Stiftung zur Krebsbekämpfung
- Erwin Braun Stiftung Basel
- Henriette Dubach Stiftung
- Innova Krankenkasse

3. Routine Analyses

3.1 Overview

The SCCR registers all tumours diagnosed and treated in Switzerland, classified according to the ICCC-3 and Langerhans cell histiocytoses (LCH) in patients aged 0 to 20 years at time of diagnosis. This annual report covers the time period from 1st January 1976 until 31st December 2013. The additional disorders, which are registered since 2014 (see inclusion criteria under paragraph 2.3), have not been included in the following analyses. Incidence rates are calculated based on the number of primary neoplasms (cases). The number of cases slightly exceeds the number of patients because patients with more than one primary tumour diagnosed before age 20 years are counted separately for each new tumour.

The section on routine analyses includes three chapters:

Chapter 3.2 presents data on all cases registered in the SCCR. This includes cases resident in Switzerland or abroad, who were diagnosed or treated in Switzerland.

Chapter 3.3 presents data on cases resident in Switzerland, aged 0 to 14 years at diagnosis. This correspondents to the age group usually covered in international publications. Therefore, tables and figures can be compared with data from other countries. Because registration in Switzerland is more than 95% complete for this age range with estimated incidence and survival rates close to their true value.

Chapter 3.4 presents data on cases resident in Switzerland, aged 15 to 20 years at diagnosis. Patients of this age group are treated in a large number and variety of clinics and therefore registration is less complete. Ultimately, incidence rates cannot be calculated for this age group.

3.2 All cases registered in the SCCR (N=8957)

This chapter describes data from all cases diagnosed 1976-2013, resident in Switzerland or abroad, diagnosed or treated in Switzerland (N=8957).

Up to 31st December 2013, a total of 8957 cases classifiable according to the ICCC-3, or Langerhans cell histiocytoses (LCH), have been registered in the SCCR. These tumours were diagnosed in 8846 patients. Among these, 8735 patients had only one primary neoplasm, 110 patients had two primary neoplasms and 2 patients had three primary neoplasms at age 0-20 years.

The SCCR started in 1976. Initially, only patients aged 0 to 15 years who participating in clinical trials were registered. Non-trial patients have been included since 1981, resulting in a significant increase in the number registered. In the early 1990s, the introduction of the first electronic database further increased case registration. Since then, annual registration has remained constant (**Figure 1**).

In the last five years (2009-2013), a total of 1284 newly diagnosed cases were registered; among them 1144 cases in Swiss residents (**Table 1**).

Swiss residents account for 7947 (89%) of all cases and foreign residents for 1010 (11%) cases (**Table 2**). Foreign residents make up 40% (156/239) of all retinoblastoma patients. This is due to the international reputation of the Jules Gonin Hospital in Lausanne, which is the national centre for retinoblastoma treatment but also attracts many patients from abroad.

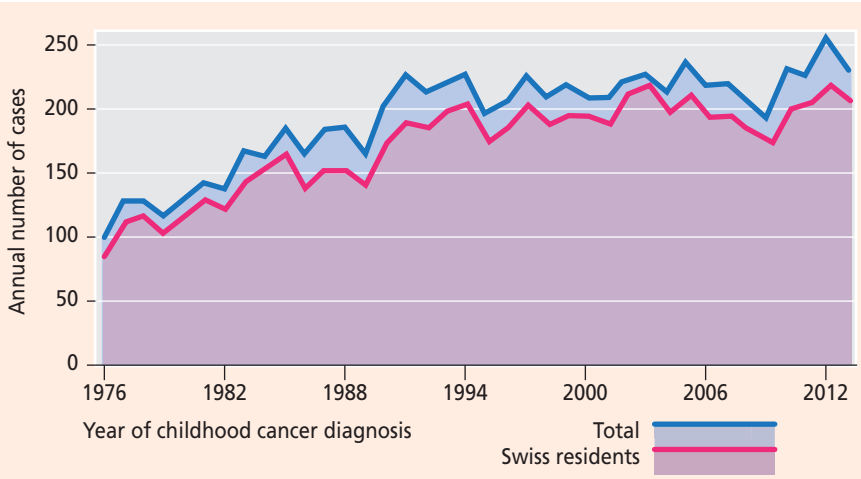


Figure 1
Annual number of registered cases over time
Swiss and foreign residents, age at diagnosis 0-14 years; period of diagnosis 1976-2013; all diagnoses (ICCC-3 or Langerhans cell histiocytosis); N=7216

Table 1
Total number of cases registered in the SCCR, by period of diagnosis

	All patients residents		Swiss residents		Foreign	
Year of diagnosis	Age at diagnosis (years)		Age at diagnosis (years)		Age at diagnosis (years)	
	0-14	15-20	0-14	15-20	0-14	15-20
1976 - 1983	995	227	870	204	125	23
1984 - 1988	862	229	737	207	125	22
1989 - 1993	1015	240	868	210	147	30
1994 - 1998	1057	297	940	264	117	33
1999 - 2003	1075	268	995	241	80	27
2004 - 2008	1082	326	966	301	116	25
2009 - 2013	1130	154	995	149	135	5
	7216	**1741**	**6371**	**1576**	**845**	**165**

Swiss and foreign residents, age at diagnosis 0-20 years; period of diagnosis 1976-2013; all diagnoses (ICCC-3 or Langerhans cell histiocytoses); N=8957

Table 2
Total number of cases registered in the SCCR, by country of residence

	Age at diagnosis (years)					
	All ages (0-20)		Children (0-14)		Adolescents (15-20)	
Country of residence	n	%	n	%	n	%
Switzerland	7947	88,7	6371	88,3	1576	90,5
Foreign countries	1010	11,3	845	11,7	165	9,5
Europe	685	7,6	588	8,1	97	5,6
• Neighbouring countries	394	4,4	335	4,6	59	3,4
- Austria	12	0,1	11	0,2	1	0,1
- France	133	1,5	101	1,4	32	1,89
- Germany	78	0,9	73	1,0	5	0,3
- Italy	170	1,9	149	2,1	21	1,2
- Liechtenstein	1	0,0	1	0,0	0	0,0
• Other European countries	291	3,2	253	3,5	38	2,2
Middle East	32	0,4	26	0,4	6	0,3
North Africa	156	1,7	124	1,7	32	1,8
Other African countries	49	0,5	41	0,6	8	0,5
All other countries	55	0,6	47	0,7	8	0,5
Abroad	33	0,4	19	0,3	14	0,9
TOTAL	**8957**	**100%**	**7216**	**100%**	**1741**	**100%**

Swiss and foreign residents, age at diagnosis 0-20 years; period of diagnosis 1976-2013; all diagnoses (ICCC-3 or Langerhans cell histiocytoses); N=8957

3.3 Swiss residents aged 0-14 years at diagnosis (N=6371)

This chapter reports on cases aged 0-14 years and resident in Switzerland at diagnosis with a tumour coded according to ICCC-3 or a Langerhans cell histiocytoses. Results for this age group can be compared directly to data from other countries.

Diagnoses

The International Classification of Childhood Cancer (ICCC-3) distinguishes 12 groups of cancers (**Table 3**). The most commons are leukaemias (33% of all cancers), followed by tumours of the central nervous system (20%; especially brain tumours); and lymphomas (12%). Other cancers arise from embryonic tissue. These include neuroblastoma (7%) from primitive neural tissue, nephroblastoma (5%) from renal tissue, hepatoblastoma (1%) in the liver, germ cell tumours (3%), and retinoblastoma (2%).

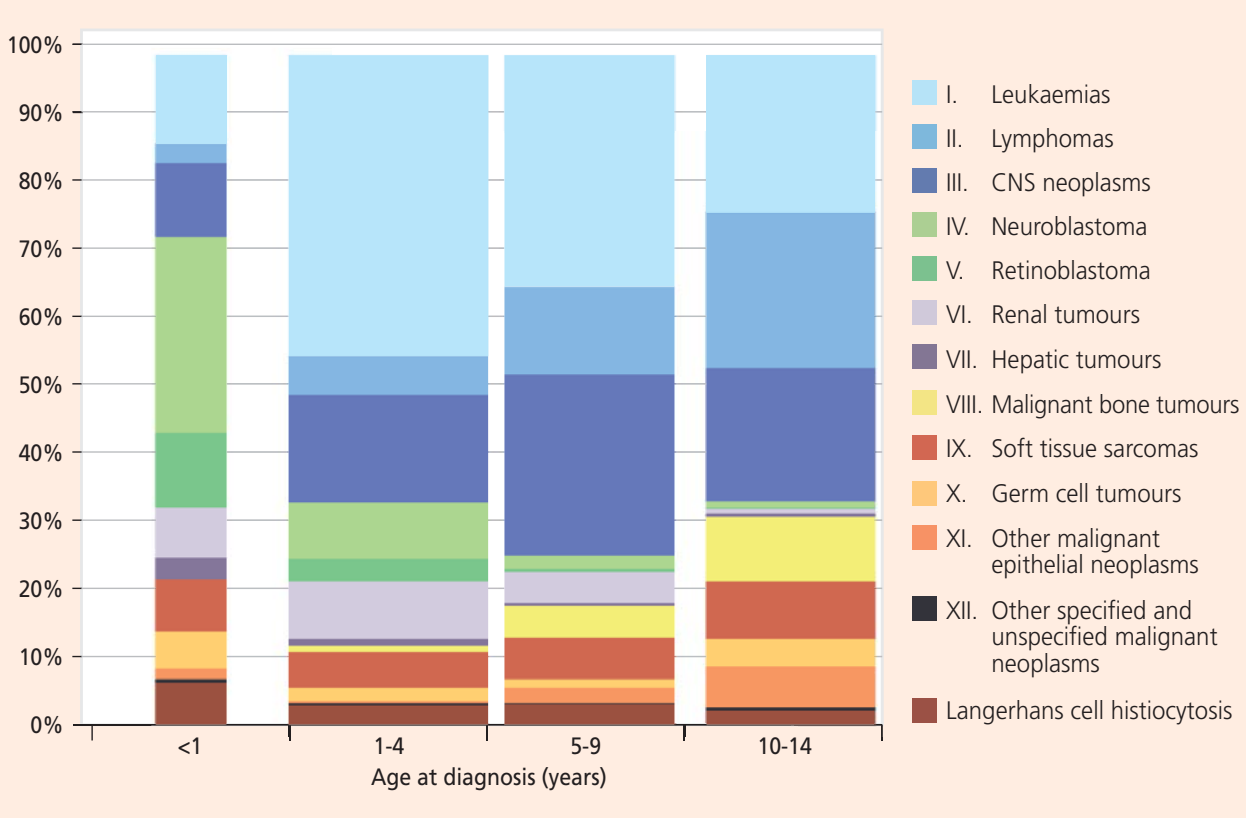
Germ cell tumours may arise in the gonads (ovaries and testes), or in other sites, such as the brain (intracranial germ cell tumours). Soft tissue sarcomas (7%), and malignant bone tumours (4%) arise from abnormal connective tissue. Occasionally, children also develop carcinomas such as melanomas or other rare tumours (3%). Langerhans cell histiocytosis (3%) is officially not counted as a malignant disease. But as children with this disease are treated similarly to those with cancer and in rare cases also die, they are recorded in the Swiss Childhood Cancer Registry. The relative frequency of the different tumour types varies with age (**Table 3** and **Figure 2**).

Table 3 Main diagnostic groups according to ICCC-3, by age at diagnosis

		All children		By age at diagnosis (years)							
				<1		1-4		5-9		10-14	
	Diagnosis	n	%	n	%	n	%	n	%	n	%
I	Leukaemias, myeloproliferative diseases and myelodysplastic diseases	2103	33,0	83	13,3	1006	45,0	592	34,6	422	23,4
II	Lymphomas and reticuloendothelial neoplasms	790	12,4	19	3,0	127	5,7	224	13,1	420	23,3
III	Central nervous system neoplasms	1247	19,6	68	10,9	360	16,1	463	27,1	356	19,8
IV	Neuroblastoma and other peripheral nervous cell tumours	421	6,6	183	29,2	187	8,4	33	1,9	18	1,0
V	Retinoblastoma	155	2,4	70	11,2	75	3,4	8	0,5	2	0,1
VI	Renal tumours	327	5,1	46	7,3	190	8,5	79	4,6	12	0,7
VII	Hepatic tumours	61	1,0	21	3,4	24	1,1	7	0,4	9	0,5
VIII	Malignant bone tumours	277	4,3	0	0,0	19	0,9	82	4,8	176	9,8
IX	Soft tissue and other extraosseous sarcomas	426	6,7	48	7,7	122	5,5	104	6,1	152	8,4
X	Germ cell tumours, trophoblastic tumours and neoplasms of gonads	175	2,7	35	5,6	41	1,8	24	1,4	75	4,2
XI	Other malignant epithelial neoplasms and malignant melanomas	167	2,6	10	1,6	9	0,4	38	2,2	110	6,1
XII	Other specified and unspecified malignant neoplasms	16	0,3	3	0,5	5	0,2	1	0,1	7	0,4
	Langerhans cell histiocytosis	206	3,2	40	6,4	69	3,1	56	3,3	41	2,3
	Total	**6371**	**100%**	**626**	**100%**	**2234**	**100%**	**1711**	**100%**	**1800**	**100%**

Swiss residents; age at diagnosis 0-14 years; period of diagnosis 1976-2013; all diagnoses (ICCC-3 or langerhans cell histiocytosis) ; N=6371

Figure 2
Main diagnostic groups according to ICCC-3, by age at diagnosis



Follow-up information

The SCCR collects follow-up information for patients in several ways:

1. **Clinical follow-up** is any contact the patient has with the paediatric oncology and haematology centre. Annual clinical follow-up care in paediatric centres usually ends 5-10 years after diagnosis. Then the patient is officially discharged or referred to an adult oncology centre. Alternatively clinical follow-up also ends, as soon as the patient dies.
2. **Long-term epidemiological follow-up** for vital status, subsequent neoplasms and current health employs four complementary approaches:
   - **Vital status** and **current address** are updated by contacting municipal population registers. Vital status is known for most cases: among the 6371 patients, 1577 (25%) have died, and 4794 (75%) are still alive (**Table 4**). Among these, most (4338) have been followed-up during the past 5 years, 314 (7%) have last been followed up between 2004 and 2008, and only 142 (3%) before 2004. Among the latter, 92 are lost to follow-up, because they moved abroad.
   - **Causes of death** are retrieved from Swiss mortality statistics by record linkage.
   - **Second primary neoplasms** are notified via paediatric oncology and haematology centres, detected by regular comparison with cantonal (regional) cancer registries in Switzerland, or self-reported by survivors and then validated with pathology reports.
   - **Morbidity and quality of life** are assessed by paper questionnaires to survivors in the Swiss Childhood Cancer Survivor Study and Childhood Cancer Follow-up Study (SCCSS & CCFU, **Chapter 4**).

Table 4 Follow-up information available in the SCCR

		n	%
Alive	**Total**	**4794**	**75%**
	Last follow-up after 2008	4338	
	Last follow-up 2004-2008	314	
	Last follow-up before 2004	142	
Deceased		**1577**	**25%**
Total		**6371**	**100%**

Swiss residents; age at diagnosis 0-14 years; period of diagnosis 1976-2013; all diagnoses (ICCC-3 or Langerhans cell histiocytosis); N=6371

Survival

Long-term survival has improved significantly over the last decades (**Figure 3**).

Ten-year survival increased from 61% in children diagnosed between 1976 and 1983, to 70% in children diagnosed between 1984-1993, 77% in children diagnosed between 1994 and 2003, and 83% in children diagnosed within the last decade (2004-2013).

Survival varied widely between diagnostic groups. **Figure 4** presents survival by diagnostic group according to ICCC-3 in children diagnosed between 1994 and 2013. Of 3896, 756 (19%) have died. The following numbers describe five-year survival for each main diagnostic group: 100% for Langerhans cell histiocytoses; 96% for germ cell tumours; 92% for lymphoma; 91% for renal tumours; 96% for retinoblastoma; 86% for malignant bone tumours; 83% for children with leukaemia; 74% for soft tissue sarcomas; 72% for central nervous system neoplasms; 66% for hepatic tumours and 63% for neuroblastoma.

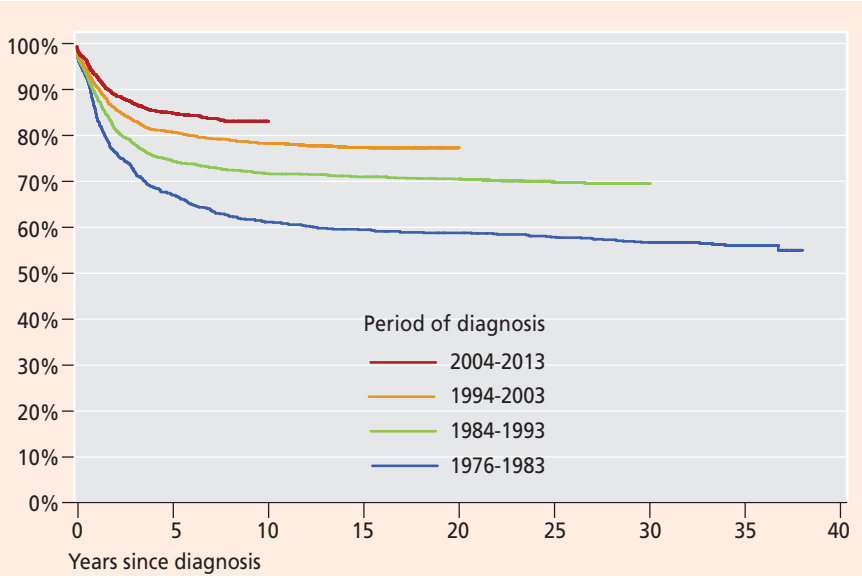


Figure 3
Survival of patients in the SCCR, by period of diagnosis

Swiss residents; age at diagnosis 0-14 years; period of diagnosis 1976-2013; all diagnoses (ICCC-3 or Langerhans cell histiocytoses); N=6371; adjusted for sex, age at diagnosis and ICCC-3 groups

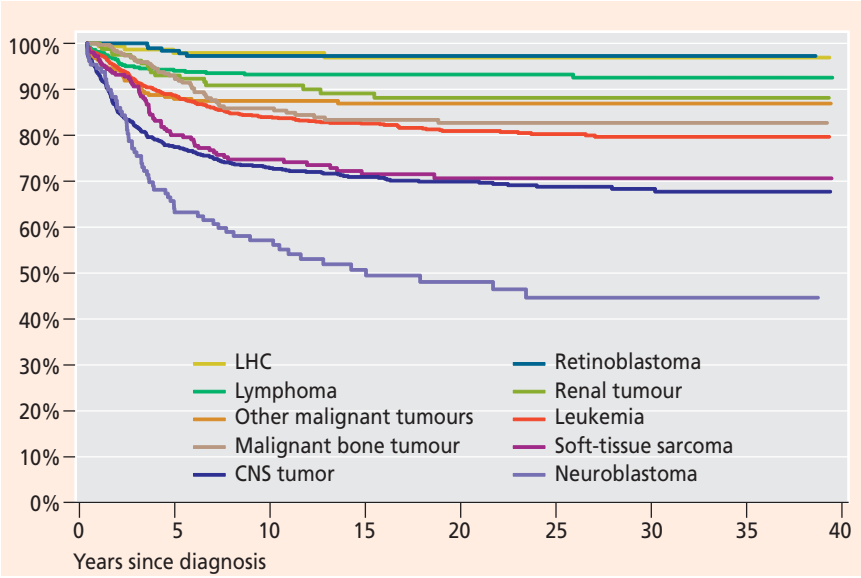


Figure 4
Survival of patients by diagnostic groups according to ICCC-3

Swiss residents; age at diagnosis 0-14 years; period of diagnosis 1994-2013 all diagnoses (ICCC-3 or Langerhans cell histiocytoses); N=3896; adjusted for sex and age at diagnosis

Cancer incidence (2004-2013) in Switzerland, for children aged 0-14 years at diagnosis

Table 5 describes the tumours registered in the SCCR during the last ten years (2004-2013). Diagnoses are coded according to ICCC-3, most tumours were more common in boys than in girls, with the exception of neuroblastoma, retinoblastoma, nephroblastoma, germ cell tumours, and other malignant epithelial neoplasms including malignant melanomas.

The age-standardised incidence (according to the European standard population) of any childhood cancer (not including Langerhans cell histiocytoses) was 15.9 per 100,000 person-years. Incidence was highest among children aged less than 1 year with 23.4 cases per 100,000 person-years (boys 22.5, girls 24.4). Incidence was lowest in 9 year olds with 9.1 cases per 100,000 person-years (boys 9.3, girls 8.8) (**Figure 5** shows crude incidence rates in Swiss residents; age at diagnosis 0-14 years; period of diagnosis 1994-2013; all diagnoses (ICCC-3 but not including Langerhans cell histiocytosis); N=3757, **Figure 6** shows age- and sex-specific incidence rates for age 0-14).

Table 5 – Childhood cancer diagnosed in Switzerland 2004-2013: number of cases, relative frequency, sex ratio, median age at diagnosis and incidence standardised according to the European standard population, by diagnostic groups according to ICCC-3

Swiss residents; age at diagnosis 0-14 years, period of diagnosis 2004-2013, all diagnoses (ICCC-3 or Langerhans cell histiocytosis); N=1961

	Diagnosis	n	Relative frequency	Sex ratio (male:female)	Age at Dx (Median)	Incidence*
I	**Leukaemias, myeloproliferative diseases and myelodysplastic diseases**	**645**	**33,9**	**1,5**	**4,9**	**5,4**
	a. Lymphoid leukaemias	519	80,5	1,5	4,6	4,4
	b. Acute myeloid leukaemias	80	12,4	1,9	6,3	0,7
	c. Chronic myeloproliferative diseases	7	1,1	6,0	10,0	0,1
	d. Myelodysplastic syndrome and other myeloproliferative diseases	31	4,8	2,9	7,0	0,3
	e. Unspecified and other specified leukaemias	8	1,2	0,6	4,6	0,1
II	**Lymphomas and reticuloendothelial neoplasms**	**216**	**11,4**	**1,7**	**10,7**	**1,8**
	a. Hodgkin lymphomas	95	44,0	0,8	12,7	0,8
	b. Non-Hodgkin lymphomas (except Burkitt lymphoma)	62	28,7	2,6	9,0	0,5
	c. Burkitt lymphoma	53	24,5	6,6	6,9	0,4
	d. Miscellaneous lymphoreticular neoplasms	6	2,8	0,5	1,1	0,1
	e. Unspecified lymphomas	0	NA	NA	NA	NA
III	**CNS and miscellaneous intracranial and intraspinal neoplasms**	**417**	**21,9**	**1,1**	**7,0**	**3,5**
	a. Ependymomas and choroid plexus tumour	40	9,6	1,2	2,7	0,3
	b. Astrocytomas	169	40,5	1,2	7,2	1,4
	c. Intracranial and intraspinal embryonal tumours	83	19,9	1,4	6,5	0,7
	d. Other gliomas	51	12,2	1,0	6,5	0,4
	e. Other specified intracranial and intraspinal neoplasms	64	15,3	0,9	11,6	0,5
	f. Unspecified intracranial and intraspinal neoplasms	10	2,4	1,5	7,8	0,1
IV	**Neuroblastoma and other peripheral nervous cell tumours**	**120**	**6,3**	**1,0**	**1,3**	**1,0**
	a. Neuroblastoma and ganglioneuroblastoma	120	100,0	1,0	1,3	1,0
	b. Other peripheral nervous cell tumours	0	NA	NA	NA	NA
V	**Retinoblastoma**	**36**	**1,9**	**0,6**	**1,1**	**0,3**
VI	**Renal tumours**	**95**	**5,0**	**0,9**	**3,4**	**0,8**
	a. Nephroblastoma and other nonepithelial renal tumours	90	94,7	0,9	3,2	0,8
	b. Renal carcinomas	5	5,3	0,7	12,8	0,0
	c. Unspecified malignant renal tumours	0	NA	NA	NA	NA
VII	**Hepatic tumours**	**17**	**0,9**	**2,4**	**1,6**	**0,1**
	a. Hepatoblastoma	15	88,2	2,0	1,6	0,1
	b. Hepatic carcinomas	2	11,8	7,0	0,0	0,0
	c. Unspecified malignant hepatic tumours	0	NA	NA	NA	NA

* Incidence: newly diagnosed tumours in a one year time period per 100,000 persons (person-years)

Table 5 Continued

Diagnosis	n	Relative frequency	Sex ratio (male:female)	Age at Dx (Median)	Incidence*
VIII Malignant bone tumours	**82**	**4,3**	**1,1**	**11,0**	**0,7**
a. Osteosarcomas	39	47,6	0,9	11,2	0,3
b. Chondrosarcomas	0	NA	NA	NA	NA
c. Ewing tumour and related sarcomas of bone	42	51,2	1,3	10,6	0,4
d. Other specified malignant bone tumours	0	NA	NA	NA	NA
e. Unspecified malignant bone tumours	1	1,2	0,0	14,7	0,0
IX Soft tissue and other extraosseous sarcomas	**144**	**7,6**	**1,3**	**7,5**	**1,2**
a. Rhabdomyosarcomas	78	54,2	1,3	5,3	0,7
b. Fibrosarcomas, peripheral nerve sheath tumours, and other fibrous neoplasms	10	6,9	2,3	10,9	0,1
c. Kaposi sarcoma	0	NA	NA	NA	NA
d. Other specified soft tissue sarcomas	44	30,6	1,1	11,1	0,4
e. Unspecified soft tissue sarcomas	12	8,3	2,0	0,8	0,1
X Germ cell tumours, trophoblastic tumours, and neoplasms of gonads	**58**	**3,1**	**1,2**	**6,9**	**0,5**
a. Intracranial and intraspinal germ cell tumours	14	24,1	1,8	12,2	0,1
b. Malignant extracranial and extragonadal germ cell tumours	15	25,9	0,9	0,1	0,1
c. Malignant gonadal germ cell tumours	27	46,6	1,3	11,4	0,2
d. Gonadal carcinomas	0	NA	NA	NA	NA
e. Other and unspecified malignant gonadal tumour	1	1,7	0,8	0,0	0,0
XI Other malignant epithelial neoplasms and malignant melanomas	**65**	**3,4**	**0,8**	**12,0**	**0,5**
a. Adrenocortical carcinomas	3	4,6	2,0	1,7	0,0
b. Thyroid carcinomas	13	20,0	0,3	13,4	0,1
c. Nasopharyngeal carcinomas	1	1,5	0,0	12,2	0,0
d. Malignant melanomas	18	27,7	1,3	11,0	0,2
e. Skin carcinomas	8	12,3	1,7	6,3	0,1
f. Other and unspecified carcinoma	22	33,8	0,6	12,0	0,2
XII Other and unspecified malignant neoplasms	**5**	**0,3**	**0,7**	**0,4**	**0,0**
a. Other specified malignant tumours	2	40,0	1,0	1,8	0,0
b. Other unspecified malignant tumours	3	60,0	0,5	0,4	0,0
Total (not including Langerhans cell histiocytosis)	**1900**	**100,0**	**1,3**	**6,1**	**15,9**
Langerhans cell histiocytosis	61	3,1	1,1	5,2	0,5
Total (including Langerhans cell histiocytosis)	**1961**	**100,0**	**1,3**	**6,1**	**16,4**

* Incidence: newly diagnosed tumours in a one year time period per 100,000 persons (person-years); NA: not applicable

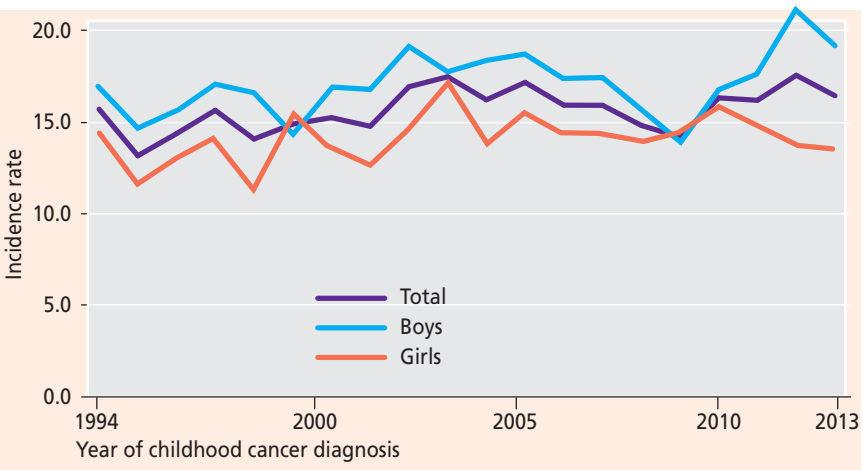


Figure 5
Crude incidence rate (per 100,000 person-years) in Switzerland, by sex and year of diagnosis for the last 20 years (1994-2013)

Swiss residents; age at diagnosis 0-14 years; period of diagnosis 1994-2013; all diagnoses (ICCC-3 but not including Langerhans cell histiocytosis); N=3856

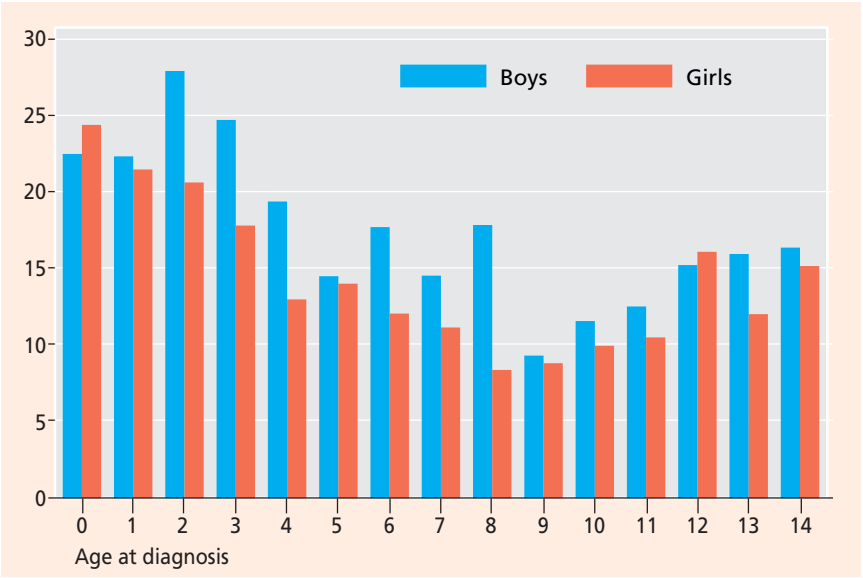


Figure 6
Age- and sex-specific incidence rates (per 100,000 person-years) in Switzerland for the last 10 years)

Swiss residents; age at diagnosis 0-14 years; period of diagnosis 2004-2013; all diagnoses (ICCC-3 but not including Langerhans cell histiocytosis); N=1961

3.4 Swiss residents aged 15-20 years at diagnosis (N=450)

Table 6 describes the tumours registered in the last ten years (2004-2013) diagnosed in adolescent patients (aged 15-20 years at diagnosis, N=450). Because data on adolescents are currently not complete within the SCCR, we do not present incidence rates. In adolescents the sex ratio is closer to 1 than in those aged 0-14 years at diagnosis.

Table 6 – Adolescent cancer diagnosed in Switzerland 2004-20013: number of cases, relative frequency, sex ratio and median age at diagnosis

Age at diagnosis 15-20 years, period of diagnosis 2004-2013, all diagnoses (ICCC-3 or Langerhans cell histiocytosis); N=450

	Diagnosis	n	Relative frequency	Sex ratio (male:female)	Age at Dx (Median)
I	**Leukaemias, myeloproliferative diseases and myelodysplastic diseases**	**58**	**12,9**	**1,9**	**16,1**
	a. Lymphoid leukaemias	34	58,6	2,1	16,0
	b. Acute myeloid leukaemias	16	27,6	1,3	16,2
	c. Chronic myeloproliferative diseases	4	6,9	3,0	18,1
	d. Myelodysplastic syndrome and other myeloproliferative diseases	4	6,9	3,0	16,7
	e. Unspecified and other specified leukaemias	0	NA	NA	NA
II	**Lymphomas and reticuloendothelial neoplasms**	**116**	**25,9**	**0,8**	**16,7**
	a. Hodgkin lymphomas	79	68,1	0,8	16,6
	b. Non-Hodgkin lymphomas (except Burkitt lymphoma)	32	27,6	0,8	17,0
	c. Burkitt lymphoma	4	3,4	1,0	18,4
	d. Miscellaneous lymphoreticular neoplasms	1	0,9	0,0	16,6
	e. Unspecified lymphomas	0	NA	NA	NA
III	**CNS and miscellaneous intracranial and intraspinal neoplasms**	**80**	**17,9**	**1,0**	**16,4**
	a. Ependymomas and choroid plexus tumour	5	6,3	0,3	18,0
	b. Astrocytomas	28	35,0	0,6	16,4
	c. Intracranial and intraspinal embryonal tumours	16	20,0	1,3	16,1
	d. Other gliomas	9	11,3	2,0	16,8
	e. Other specified intracranial and intraspinal neoplasms	22	27,5	1,2	16,3
	f. Unspecified intracranial and intraspinal neoplasms	0	NA	NA	NA
IV	**Neuroblastoma and other peripheral nervous cell tumours**	**0**	**NA**	**NA**	**NA**
	a. Neuroblastoma and ganglioneuroblastoma	0	NA	NA	NA
	b. Other peripheral nervous cell tumours	0	NA	NA	NA
V	**Retinoblastoma**	**0**	**NA**	**NA**	**NA**
VI	**Renal tumours**	**7**	**1,6**	**2,5**	**16,6**
	a. Nephroblastoma and other nonepithelial renal tumours	2	28,6	4,5	16,0
	b. Renal carcinomas	5	71,4	1,5	17,4
	c. Unspecified malignant renal tumours	0	NA	NA	NA
VII	**Hepatic tumours**	**4**	**0,9**	**3,0**	**16,0**
	a. Hepatoblastoma	0	NA	NA	NA
	b. Hepatic carcinomas	4	100,0	3,0	16,0
	c. Unspecified malignant hepatic tumours	0	NA	NA	NA
VIII	**Malignant bone tumours**	**48**	**10,7**	**1,5**	**16,3**
	a. Osteosarcomas	35	72,9	1,7	16,5
	b. Chondrosarcomas	1	2,1	0,0	15,1
	c. Ewing tumour and related sarcomas of bone	10	20,8	1,0	16,0
	d. Other specified malignant bone tumours	2	4,2	1,0	16,7
	e. Unspecified malignant bone tumours	0	NA	NA	NA

Table 6 Continued

	Diagnosis	n	Relative frequency	Sex ratio (male:female)	Age at Dx (Median)
IX	**Soft tissue and other extraosseous sarcomas**	**31**	**6,9**	**0,9**	**16,5**
	a. Rhabdomyosarcomas	13	41,9	0,9	15,9
	b. Fibrosarcomas, peripheral nerve sheath tumours, and other fibrous neoplasms	3	9,7	0,5	15,8
	c. Kaposi sarcoma	0	NA	NA	NA
	d. Other specified soft tissue sarcomas	11	35,5	0,4	17,0
	e. Unspecified soft tissue sarcomas	4	12,9	3,0	16,6
X	**Germ cell tumours, trophoblastic tumours, and neoplasms of gonads**	**32**	**7,1**	**9,7**	**17,8**
	a. Intracranial and intraspinal germ cell tumours	3	9,4	0,0	17,2
	b. Malignant extracranial and extragonadal germ cell tumours	0	NA	NA	NA
	c. Malignant gonadal germ cell tumours	27	84,4	26,0	18,0
	d. Gonadal carcinomas	2	6,3	0,0	15,7
	e. Other and unspecified malignant gonadal tumour	0	NA	0,0	NA
XI	**Other malignant epithelial neoplasms and malignant melanomas**	**71**	**15,8**	**0,7**	**18,2**
	a. Adrenocortical carcinomas	1	1,4	0,0	17,0
	b. Thyroid carcinomas	22	31,0	0,2	17,6
	c. Nasopharyngeal carcinomas	3	4,2	0,0	17,9
	d. Malignant melanomas	28	39,4	0,8	18,5
	e. Skin carcinomas	5	7,0	0,0	18,6
	f. Other and unspecified carcinoma	12	16,9	5,0	17,9
XII	**Other and unspecified malignant neoplasms**	**1**	**0,2**	**0,0**	**15,2**
	a. Other specified malignant tumours	1	100,0	0,0	15,2
	b. Other unspecified malignant tumours	0	NA	NA	NA
	Total (not including Langerhans cell histiocytosis)	**448**	**100,0**	**1,1**	**16,8**
	Langerhans cell histiocytosis	2	0,4	1,0	16,2
	Total (including Langerhans cell histiocytosis)	**450**	**100,0**	**1,1**	**16,8**

4. Research projects on childhood cancer

Current research projects of the childhood cancer registry are summarised in **Table 7**. All projects are described in more detail in the remainder of **Chapter 4**. Additional information is available from the references and from the investigators. Further, we thank the supporters for their generous contributions towards the research projects.

Table 7
Current research projects of the SCCR, summary

Project name	Senior investigator	Funding sources	Study period
Outcome research			
1 Swiss Childhood Cancer Survivor Study (SCCSS)	Von der Weid NX, Kuehni CE Kuehni CE Kuehni CE Kuehni CE, Bergstraesser E Kuehni CE, Angst R	Swiss Cancer League (KLS-2215-02-2008) Kinderkrebshilfe Schweiz Cancer League Bern Cancer League Zurich Cancer League Aarau	since 01.2006
2 Follow-up care after childhood and young adult cancer (CCFU)	Michel G	Swiss National Science Foundation (PZ00P3_121682/1)	08.2012-08.2014
3 PanCare childhood and adolescent cancer survivor care and follow-up studies (PanCareSurFup)	Kuehni CE Kuehni CE	EU FP7 PanCareSurfUp (HEALTH-F2-2010-257505) Swiss Cancer League (KFS - 02783-02-2011)	02.2011-01.2016
4 PanCare Studies in Fertility and Ototoxicity to improve Quality of Life after Cancer during Childhood, Adolescence and Young Adulthood (PanCareLIFE)	Kuehni CE	EU FP7 PanCareLife (HEALTH-F2-2013-602030) Swiss Cancer League (KFS - 3412-02-2014)	11.2013-10.2018
5 Risk of cancer and long-term mortality in children treated with growth hormone: Swiss participation in the EU FP7 project (SAGhE)	Mullis P Mullis P, Kuehni CE	EU FP 7 (HEALTH-F2-2009-223497) Swiss Cancer League (KLS - 2948-02-2012)	since 2010
6 Mortality after cancer in childhood and adolescence	Kuehni CE Kuehni CE	Swiss National Science Foundation Swiss Bridge	08.2012-08.2015
7 Fertility after Chemo- and Radiotherapy in Childhood and Adolescence, FeCt – Multicentre	Michel G	Kinderkrebshilfe Schweiz	since 2012
8 Parents of long-term childhood cancer survivors	Michel G	Swiss National Science Foundation (100019_153268 / 1) Kinderkrebshilfe Schweiz	since 2013
9 Effectiveness of transition from paediatric to adult care after childhood cancer	Michel G	Swiss Cancer League (KFS - 02631-08-2010)	04.2011-04.2014
Aetiology of childhood cancer			
10 Childhood cancer and vicinity of residence to petrol stations and roads: census-based nation wide cohort study (PETROL)	Kuehni CE	Federal Office of Public Health	06.2010-02.2013
11 Childhood cancer and geographically defined exposures in Switzerland: a census-based nationwide cohort study	Spycher BD	Federal Office of Public Health	03.2013-11.2013
12 The role of population mixing and exposure to infections in the aetiology of childhood leukaemia: a national cohort study	Spycher BD	Swiss Cancer League (KFS-3049-08-2012)	01.2013-12.2014
13 The spatial epidemiology of childhood cancer in Switzerland	Spycher BD	Swiss National Science Foundation	09.2013-08.2016

4.1 Swiss Childhood Cancer Survivor Study (SCCSS)

Background: Thanks to therapeutic improvements in the past decades, survival rates for childhood cancer now exceed 80%, leading to a growing population of long-term survivors. However, cancer and cancer treatments lead to adverse late effects and the health and quality of life of survivors are of increasing concern. In Switzerland and other countries, comprehensive data on the burden of late effects of childhood cancer and its risk factors, as well as data on the use of follow-up care in long-term survivors is scarce.

Objectives: The project investigates long-term outcomes of survivors of childhood and adolescent cancer. It studies the incidence and spectrum of various somatic and psycho-social outcomes including late mortality, second primary malignancies, somatic health and medication, mental health, educational achievements, health related quality of life, and their association with a number of risk factors (tumour, treatment modalities, demographic characteristics). Current practices of health-care provision and health behaviour in long-term survivors are also investigated.

Methods: Prospective cohort study based on the population of children and adolescents registered in the SCCR. Eligible for the study are all individuals, who have been diagnosed with cancer at age <21 years, who are 5-year survivors and still alive, and who were Swiss residents at time of diagnosis. A detailed questionnaire is sent to all participants. Questionnaire data are complemented with phone interviews to patients and validated with information from general practitioners and hospital records. For comparison, the same questionnaire is sent to siblings of childhood cancer survivors.

Rationale and significance: The existing database of the SCCR provides the rare opportunity for a nationwide study on long-term outcomes in survivors of childhood cancer. The project will increase the knowledge on the incidence of, and risk factors for late effects, and provide a summary of the current status of care in Switzerland. As many late effects can be prevented or cured if diagnosed early, this study will contribute to improving the health of current and future survivors of childhood cancer.

Current status of the project: Among 2930 eligible survivors aged 0-<16 years at diagnosis, 2235 (76%) completed the questionnaire. Among 598 contacted survivors aged 16-20 years at diagnosis, 320 (54%) replied. Of 1522 contacted siblings 866 (57%) participated. The study is ongoing and new 5 year survivors are included at regular intervals. Data are continuously analysed and published.

Study team: Kuehni CE, von der Weid NX, Michel G, Kasteler R, Sommer G, Wengenroth L, Weiss A. Institute of Social and Preventive Medicine, University of Bern;

Funding: Swiss Cancer League (Grant No KLS-01605-10-2004, KLS-2215-02-2008 and KLS-3412-02-2014), Bernese Cancer League, Cancer League Zurich, Cancer League Aargau.

Contact: Claudia Kuehni (claudia.kuehni@ispm.unibe.ch), Grit Sommer (grit.sommer@ispm.unibe.ch)

Publications (for details see publication list on page 33)**:**

- Wengenroth L. et al. Pediatr Blood Cancer. 2014
- Gianinazzi ME. et al. Care Cancer. 2014
- Gianinazzi ME. et al. Pediatr Blood Cancer. 2014
- Gianinazzi ME. et al. Psychooncology. 2013
- Rueegg CS. et al. Pediatr Blood Cancer. 2013
- Rueegg CS. et al. J Cancer Surviv. 2013
- Rebholz CE. et al. Pediatr Blood Cancer. 2012
- Kuehni CE. et al. Cancer. 2012
- Rebholz CE. et al. Br J Cancer. 2012
- Kuehni CE. et al. Int J Epidemiol. 2012
- Rueegg CS. et al. PLoS One. 2012
- Essig S. et al. PLoS One. 2012
- Rebholz CE. et al. Eur J Cancer. 2011
- Michel G. et al. Psycho-Oncology. 2011
- Michel G. et al. Journal of Clinical Oncology. 2011
- Marquis A. et al. Pediatr Blood Cancer. 2010

4.2 Follow-up Care After Childhood and Young Adult Cancer (CCFU)

Background: Treatment for cancer in children and young adults has greatly improved and most patients are being cured today. However, more than 50% of survivors of childhood cancer suffer from late-effects. To detect and treat late-effects as early as possible, many survivors should continue to attend follow-up care long after their cancer has been cured. Various models of follow-up care have been described, but so far none has been implemented in Switzerland. While follow-up care needs to be constantly updated to meet the current status of research, survivor participation is only ensured if follow-up is convenient.

Objectives: 1) To compare the advantages and disadvantages of follow-up care models currently used in Europe; 2) To determine the current availability and use of follow-up care in survivors of childhood and young adult cancers in Switzerland; and, 3) To determine the advantages and disadvantages of follow-up care models as perceived by survivors, oncologists and family practitioners, and to compare their views and opinions.

Methods: For part 1), we invited 198 clinics and follow-up programmes in Europe to complete a questionnaire survey describing the follow-up care available at their institution. For part 2), we analysed the current use of follow-up care together with the psychological well-being in childhood cancer survivors, using data from the Swiss Childhood Cancer Survivor Study (SCCSS). In part 3), a questionnaire survey assessed opinions and perspectives on both currently used and desired optimal follow-up care. The sample included childhood, adolescent and young adult cancer survivors diagnosed with cancer between 1990 and 2005 and aged <25 years, who survived for >5 years and who were aged 18+ years at the time of the study. In addition, parents of survivors aged 11-18 years, paediatric and adult oncologists and haematologists and family practitioners have completed a questionnaire.

Rationale and significance: This project provides an overview of follow-up care in Europe and will describe survivor, oncologist and family practitioner preferences for follow-up care models in Switzerland. We will determine the differences between the three groups in order to improve follow-up care and adapt it to differing preferences. The project will provide the basis for the development of a standardised model of follow-up care for childhood cancer survivors in Switzerland.

Current status of the project: All questionnaire surveys have been completed, and several papers have been published.

Study team: Michel G, Rueegg CS, Department of Health Sciences and Health Policy, University of Lucerne; Kuehni CE, Institute of Social and Preventive Medicine, University of Bern

Funding: Swiss National Science Foundation Ambizione Grant to Michel G (PZ00P3_121682 and PZ00P3_141722)

Contact: Gisela Michel (gisela.michel@unilu.ch)

Publications (for details see publication list on page 33)**:**

- Lupatsch J. et al. JAYAO. 2014
- Vetsch J. et al. Pediatr Blood Cancer. 2014
- Gianinazzi ME. et al. Support Care Cancer. 2014
- Gianinazzi ME. et al. Pediatr Blood Cancer. 2014
- Singer S. et al. Pediatr Blood Cancer. 2013
- Gianinazzi ME. et al. Psychooncology. 2013
- Essig S. et al. PLoS ONE. 2012
- Michel G. et al. Psychooncology. 2011
- Rebholz C. et al. Eur J Cancer. 2011
- Michel G. et al. Journal of Clinical Oncology. 2010

4.3 PanCare Childhood and Adolescent Cancer Survivor Care and Follow-Up Studies (PanCareSurFup)

Background: Long-term survival after childhood cancer exceeds 80%, but two thirds of survivors develop chronic conditions. Late mortality is increased as a consequence of the cancer and its treatment. More than ten years after diagnosis, deaths from second primary cancers and circulatory causes predominate. There is a need to identify avoidable risk factors for these late effects. These risk factors are being investigated within the international study PanCareSurFup, where Switzerland is one of the 11 participating European countries.

Objectives: The study investigates incidence and risk factors for second primary cancers, cardiovascular diseases and late mortality. Furthermore, guidelines for the clinical follow-up of survivors will be developed.

Methods: The Swiss cohort of 5-year survivors of childhood cancer will contribute to the pan-European cohort. Within the cohort we identify cardiovascular diseases and second primary cancers via: a) questionnaires; b) mortality records; and, c) record linkage with cantonal cancer registries (for second primary cancers). Patient-reported diseases are validated with medical records. Survivors suffering from severe cardiovascular diseases or second primary sarcomas or carcinomas are included in a nested case-control study. For those patients, we are extracting details of radio- and chemotherapy from medical records. In close collaboration with experts from across Europe, we write systematic reviews to develop evidence-based, standardised guidelines for clinical follow-up of survivors.

Rationale and significance: This research project provides a unique opportunity to study the most severe and life threatening late effects of childhood cancer in an international setting that maximises statistical power and generalisability of results. The identification of avoidable causes for cardiovascular diseases and second primary cancers will allow treatments to be adapted for new patients. The goal is to maximize cure rates with minimal long-term side effects.

Current status of project: The Swiss cohort dataset includes 4719 5-year survivors. Data on vital status, causes of death, as well as data on second primary neoplasms and cardiovascular diseases are currently being analysed. The case-control studies are ongoing and we are currently collecting detailed treatment data from medical records for survivors included in these studies.

Study team: Kuehni CE, Kuonen R, Sommer G, Schindler M, Institute of Social and Preventive Medicine, University of Bern; Michel G, Department of Health Sciences and Health Policy, University of Lucerne

Funding: European Union FP7- HEALTH 2010.2.4.1-7 (Project No. 257505). Swiss Cancer League (Grant No KFS-02783-02-2011)

Contact: Claudia Kuehni (claudia.kuehni@ispm.unibe.ch), Rahel Kuonen (rahel.kuonen@ispm.unibe.ch)

Publications (for details see publication list on page 33)**:**
Brown M. et al. Pediatr Blood Cancer. 2014
Feijen. et al. PloS one. 2014

4.4 PanCare Studies in Fertility and Ototoxicity to Improve Quality of Life after Cancer during Childhood, Adolescence and Young Adulthood (PanCareLIFE)

Background: Improved therapies and care have increased survival rates of childhood cancer in recent decades. This results in an increasing population of childhood cancer survivors. However, cancer treatments are harsh and can cause serious side-effects, such as hearing loss or infertility, which can greatly impact survivors' quality of life in the long term. PanCareLIFE is a large international study, which identifies individual risk factors for these late effects.

Objectives: The study investigates incidence, severity and the risk factors for hearing loss and infertility in childhood cancer survivors. Furthermore, it compares health-related quality of life and its determinants between countries.

Methods: The Swiss cohort of 5-year survivors of childhood cancer will be part of the pan-European cohort looking at health related quality of life, hearing loss and infertility. Within this cohort we will identify patients with hearing loss or infertility via a questionnaire. Patients with hearing loss will then be included into a nested case-control study to identify non-genetic and genetic risk factors. Patient-reported diseases will be validated via the collection of audiograms from original medical records and detailed treatment data will be collected for selected patients.

Rationale and significance: This large pan-European cohort provides a unique opportunity to study late effects such as hearing loss, infertility and their impact on health-related quality of life. The findings of this project will lead to improvements in patient care.

Current status of project: The study started in November 2013. Detailed study protocols and questionnaires for the different study aims are currently being developed.

Study team: Kuehni CE, Kuonen R, Sommer G, Kasteler R, Weiss A, Institute of Social and Preventive Medicine, University of Bern; von der Weid NX, Paediatric Oncology, University Children's Hospital Basel

Funding: European Union FP7-HEALTH-2013-INNOVATION-1 HEALTH.2013.2.4.1-3 (Project No. 602030), Swiss Cancer League (Grant No KFS-3412-02-2014)

Contact: Claudia Kuehni (claudia.kuehni@ispm.unibe.ch), Rahel Kuonen (rahel.kuonen@ispm.unibe.ch)

4.5 Risk of Cancer and Long-Term Mortality in Children Treated with Growth Hormone: Swiss Participation in the EU FP7 Project (SAGhE)

Background: Growth Hormone (GH) promotes body growth. If GH production is impaired, it can be substituted with daily injections. Growth hormone deficiency (GHD) is the most common endocrine late effect of childhood cancer treatment, especially after brain tumours and/or cranial irradiation. However, well-conducted long-term studies on the safety of GH replacement therapy are lacking, and several experimental studies raised concerns about cancer risk and long-term mortality. These questions are investigated in the European FP-7 project «Safety and Appropriateness of Growth hormone treatments in Europe» (SAGhE).

Objectives: The project investigates long-term efficacy (final height), health related quality of life (HRQoL) and long-term safety of GH-treatment in childhood, in particular the risk of cancer and/or mortality.

Methods: Cohort study based on the population of patients who were treated with GH during childhood in Switzerland since 1985. Eligible patients were identified from paediatric endocrinology centres in Switzerland; the SCCR and the Swiss Paediatric Renal Registry, and databases from pharmaceutical companies. Relevant data were extracted from hospital records. Quality of life was assessed by a questionnaire. Incident cancers were assessed via linkage with the SCCR and cantonal cancer registries. Date and place of death were obtained via municipal population registers, cause of death from the mortality statistics. Risk of cancer and mortality in the cohort were compared to the risk in the general population by calculating standardized incidence ratios and standardized mortality ratios.

Rationale and significance: The project describes the use of GH in Switzerland and analyses long-term safety in the context of a high-quality international collaborative study. Results will likely influence future recommendations for treatment with GH in children.

Current status of project: We identified 1884 patients treated with GH during childhood. Patients older than 18 years were included in the SAGhE study (N=754). We assessed health related quality of life for patients over 18 years via a postal questionnaire. A total of 687 patients were eligible and 415 (60%) replied. All data have been sent to work package leaders and publications are expected in 2015.

Study team: Kuehni CE, Sommer G, Kuonen R. Institute of Social and Preventive Medicine, University of Bern; Mullis PE. University Children's Hospital, Inselspital Bern.

Funding: European Union FP7 (Grant No HEALTH-F2-2009-223497), Swiss Cancer League (Grant No KLS-02586-02-2010 and KLS-2948-02-2012).

Contact: Claudia Kuehni (claudia.kuehni@ispm.unibe.ch), Grit Sommer (grit.sommer@ispm.unibe.ch)

4.6 Mortality and Second Primary Cancers after Cancer in Childhood and Adolescence

Background: Despite improved cure rates, childhood cancer remains the most common disease related cause of death in childhood. In the first 10 years after diagnosis the primary cancer is the main cause of death, but thereafter deaths from second primary cancers and chronic diseases predominate.

Objectives: This project aims to: 1) analyse survival and factors associated with survival after cancer in childhood; 2) analyse total and cause-specific mortality, including late mortality (>5 years after diagnosis of cancer) after cancer in childhood.

Methods: This study uses data from all children diagnosed with cancer in Switzerland. Vital status and date of death are updated via municipal population registries. Cause of death is available from the Swiss mortality statistics. We estimate survival at 5, 10 and 20 years after diagnosis, overall and stratified by diagnosis, and analyse time trends in survival. We examine determinants of survival (sex, type of childhood cancer, tumour histology, age at diagnosis, treatment modalities, region of residence, socio-economic position). For aim 2 we calculate overall and cause-specific standardized morality ratios (SMR) and absolute excess risks (AER), cumulative mortality and risk factors for specific causes of death.

Rationale and significance: This project provides the first national data on survival and long-term mortality after cancer in childhood in Switzerland. Knowledge about avoidable risk factors for premature death will help to develop improved treatments.

Current status of project: Analysis is ongoing and 2 publications are being written.

Study team: Kuehni CE, Schindler M, Institute of Social and Preventive Medicine University of Bern; Michel G, Department of Health Sciences and Health Policy, University of Lucerne

Funding: Swiss National Science Foundation (PDFMP3_141775), Swiss Bridge

Contact: Claudia Kuehni (claudia.kuehni@ispm.unibe.ch), Matthias Schindler (matthias.schindler@ispm.unibe.ch)

Publications: Expected for 2015

4.7 Fertility after Chemo- and Radiotherapy in Childhood and Adolescence, FeCt – Multicentre Offspring Study

Background: Similar to the general population many former childhood cancer patients wish to have children. However, many survivors worry that their own children might develop cancer or could have other health problems. These fears can affect the quality of life and family planning. Previous studies found no increased risk for genetic diseases or cancers. However, most studies only included small numbers of survivors with their own children. Therefore, the SCCR participates in an international multicentre study including Germany [Principal Investigator], Austria, Poland, Czech Republic and Switzerland.

Objectives: In order to provide better information and education of patients and survivors of childhood cancer we aim to answer the following questions: 1. Is there a difference in the general health status of the offspring of former childhood cancer patients compared to children in the general population? 2. How concerned are former childhood cancer patients regarding their children? 3. How healthy do children of former childhood cancer patients grow up?

Methods: In this cross-sectional study we include all former patients registered at the SCCR who were diagnosed with cancer under age 16 years, were Swiss residents at diagnosis, are now at least 18 years old and have own children. In addition, we invite siblings of participating survivors to complete a questionnaire for their children. The questionnaire was developed in Germany and includes questions on the health status of the offspring, and concerns of survivors regarding their children.

Rationale and significance: The proposed study will provide a better basis for the education of former, current and future patients. Fears of former cancer patients can be addressed and reduced if valid and adequate information is available. Where required, preventive measures to improve health impairment in offspring can be taken.

Current status of the project: We are currently preparing the questionnaire survey.

Study team: Michel G, Vetsch J, Rueegg CS, Department of Health Sciences and Health Policy, University of Lucerne

Funding: Kinderkrebshilfe Schweiz.

Contact: Gisela Michel (gisela.michel@unilu.ch), Janine Vetsch (janine.vetsch@unilu.ch)

4.8 Parents of Long-Term Childhood Cancer Survivors

Background: When a child is diagnosed with cancer, parents are confronted with the potential fatality of the disease. They experience a highly stressful time, which may affect their psychological well-being, their relationship as a couple, and with their children. Additionally, because of prolonged absence from work, they may experience an economic burden. However, for many parents distress is not over with the end of treatment and the cure of their child. Parents may suffer from a variety of psychological problems such as depression, anxiety or post-traumatic stress symptoms. Uncertainty about their child's health and worries about a possible relapse or late effects may negatively affect parents individually or as a couple. So far, late outcomes of childhood cancer in parents have mostly been studied in small samples and only within a short time frame after the end of treatment.

Objectives: We aim to 1) describe psychological and socio-demographic outcomes, as well as needs in parents of long-term childhood cancer survivors and compare them with parents of the general population, 2) evaluate associations of these outcomes with the clinical characteristics of the child's disease and the child's own late outcomes and 3) provide Swiss norm-data for established and frequently used instruments on quality of life, psychological distress and post-traumatic stress.

Methods: We will include all parents whose children were diagnosed with cancer under age 16 years, who were Swiss residents at diagnosis, who survived for 5 years or more, and are currently alive and aged 20 years or older. Additionally, we will select a random sample of parents from the general population. Parents of survivors will first be contacted by paediatric oncologists from the original treating clinic. All parents will receive a questionnaire package from the study centre. Clinical information on the cancer and treatment are available from the SCCR, and information about survivors' health from the Swiss Childhood Cancer Survivor Study.

Rationale and significance: Several large cohort studies among childhood cancer survivors have improved our knowledge on their late outcomes and well-being. However, while most survivors get on with their life after cancer, many parents remain affected by their experience long after their child reaches adulthood. The proposed study will be the first population-based study among parents of long-term survivors of childhood cancer and will shed light on their psychological well-being, social outcomes and the needs they have for their children and themselves.

Current status of the project: The new questionnaire including questions on quality of life, post-traumatic growth, family bonding and social consequences has been developed and we are currently preparing the documents for the submission to the ethics committee.

Study team: Michel G, Vetsch J, Rueegg CS, Department of Health Sciences and Health Policy, University of Lucerne

Funding: Swiss National Science Foundation (Grant-No: 100019_153268 / 1), Kinderkrebshilfe Schweiz.

Contact: Gisela Michel (gisela.michel@unilu.ch), Janine Vetsch (janine.vetsch@unilu.ch)

4.9 Effectiveness of Transition from Paediatric to Adult Care after Childhood Cancer

Background: Transition from paediatric to adult care is a crucial step in many chronic diseases of childhood. Treatments in paediatric oncology have improved over the past decades; now about 80% of patients survive to adulthood. However, 60% suffer from adverse somatic or psychosocial late effects from the cancer and its treatments and necessitate long-term follow-up. Generally, follow-up is well organised during the first 5-10 years after diagnosis, and often occurs in the context of a clinical trial. However, transfer of patients to adult care often fails, and survivors may be lost to follow-up or continue to visit their paediatric institution despite their adult status and changing needs.

Objectives: The project aims to: 1) determine the frequency of follow-up in childhood cancer survivors when they are in paediatric care; 2) describe transfer modalities; 3) describe the health care providers involved in follow-up and transfer; 4) determine factors associated with successful transfer; and 5) describe the advantages and disadvantages of different kinds of follow-up for survivors, families and health care providers from paediatric and adult wards.

Method: This study analyses information collected from medical records on follow-up care, transitional care and transfer to adult care. Additional information on current follow-up, socio-economic characteristics and late effects comes from two separate, on-going questionnaire studies (Swiss Childhood Cancer Survivor Study and Childhood Cancer Follow-Up Study).

Rationale and Significance: The available information will be used to develop the first national guidelines for the transition of childhood cancer survivors. In addition, results will provide a basis for the improvement of transitional care for other chronic diseases.

Current status of project: All data have been collected and are now being analysed.

Study team: Michel G, Gianinazzi ME, Department of Health Sciences and Health Policy, University of Lucerne

Funding: Swiss Cancer League (Grant No KFS-02631-08-2010)

Publications: Expected for 2015.

Contact: Gisela Michel (gisela.michel@unilu.ch)

4.10 Childhood Cancer and Vicinity of Residence to Petrol Stations and Roads: Census-Based Nationwide Cohort Study (PETROL)

Background: Benzene is a common air-pollutant; it is haematotoxic and an established human carcinogen. Its association with acute myeloid leukaemia is well documented in adults but data on children are scarce. To our knowledge, no cohort studies have investigated potential associations between benzene exposure and childhood cancer in children.

Objective: To examine whether 1) residence in the proximity of petrol stations, motor vehicle service stations or major roads, and 2) parental profession-related exposure to benzene are associated with a higher risk of cancer, particularly leukaemia, in children and adolescents.

Methods: The study includes all children born between January 1985 and December 2008, aged 0-15 years at diagnosis of cancer or leukaemia and resident in Switzerland (N=5300). Data on these children were obtained from the Swiss National Cohort (SNC), a long-term, census-based cohort that includes all Swiss inhabitants. Diagnosed cases of cancer were identified from the SCCR. Geocoded places of residence were used to assess proximity to petrol stations, motor vehicle service stations and major roads. We considered place of residence at birth and at diagnosis separately. Data on parental occupation during the 1990 and 2000 censuses were obtained from the SNC. Using a job exposure matrix we identified children whose parents were exposed to benzene at work. The data were analysed using Poisson regression and Cox proportional hazard models, adjusting for a range of potential confounders including socio-economic status, background ionizing radiation and birth weight.

Rational and Significance: Traffic-related pollution, including benzene, and its effects on health are a major public health problem because a substantial proportion of the population is exposed. This unique, large-scale study will help clarify whether traffic-related air pollution and exposure to benzene in particular, contribute to the incidence of childhood cancer in the general population.

Current status of project: Analyses have been completed and results are currently being written up and submitted for publication.

Study team: Spycher BD, Kuehni CE. Institute of Social and Preventive Medicine, University of Bern.

Funding: Swiss Federal Office of Public Health (BAG 10.002946)

Contact: Ben Spycher (ben.spycher@ispm.unibe.ch), Claudia Kuehni (claudia.kuehni@ispm.unibe.ch)

4.11 Childhood Cancer and Geographically Defined Exposures in Switzerland: A Census-Based Nationwide Cohort Study

Background: Ionising radiation is the only environmental exposure that has been clearly linked to cancer in children. It is, however, still unclear whether the dose-response relationships found in studies of persons exposed to moderate or high doses can be extrapolated to the lower doses from background radiation.

Objective: To examine the risk of cancer in children and adolescents associated with exposure to background ionising radiation from cosmic and terrestrial sources.

Methods: The study included all children born between January 1985 and December 2008, aged 0-15 years at diagnosis and resident in Switzerland (N=5300). Data on these children were obtained from the Swiss National Cohort (SNC), a long-term, census-based cohort that includes all Swiss inhabitants. Diagnosed cases of cancer were identified from the SCCR. Based on previously developed radiation maps we determined dose rates of ionising radiation (unit: nSv/h) from cosmic rays and terrestrial gamma rays at places of residence. We considered both the place of residence at birth and at diagnosis. We investigated the following outcomes: all childhood cancer, leukaemia, acute lymphoid leukaemia, acute myeloid leukaemia, and tumours of the central nervous system (CNS). Associations between outcomes and radiation dose rates were assessed using Poisson regression and Cox proportional hazard models, adjusting for a range of potential confounders including socio-economic status, proximity to highways and power lines, and birth weight.

Rationale and Significance: It is well known that ionizing radiation at moderate to high doses causes cancer in humans. What remains unclear is whether protracted exposure to radiation at low dose rates, such as exposure to natural background radiation, contributes to cancer risk in the population at large. With the SCCR and the SNC we have the rare opportunity to study exposure to natural background radiation in a nationwide cohort study. In addition, exposure to natural background radiation has a relatively high variation in Switzerland, because of differences in altitude between residential locations.

Current status of project: The analyses have been completed and a manuscript has been submitted for publication.

Study team: Spycher BD, Kuehni CE. Institute of Social and Preventive Medicine, University of Bern.

Funding: Swiss Federal Office of Public Health (BAG 12.008357)

Contact: Ben Spycher (ben.spycher@ispm.unibe.ch), Claudia Kuehni (claudia.kuehni@ispm.unibe.ch)

Publications:

Spycher BD et al. Environ Health Perspect. in press. 2014

4.12 The Role of Population Mixing and Exposure to Infections in the Aetiology of Childhood Leukaemia: A National Cohort Study

Background: Leukaemia is the most important cancer among children in industrialized countries. Infections may play a role: the incidence of acute lymphoic leukaemia (ALL) is higher in resource-rich countries, where infections early in life are less common compared to resource-poor settings; there is a sharp peak in incidence at 2-5 years of age; local clusters of cases have been described and there is seasonal variation in the diagnosis of ALL. Kinlen proposed that population mixing, i.e. large influxes of people into previously isolated areas, could explain clusters of childhood leukaemia. Childhood leukaemia may thus be a rare response to a common, yet unidentified, infection. Greaves proposed the delayed-immune hypothesis as an explanation for the peak incidence of ALL at 2-5 years: a lack of exposure to infections in early life could predispose the immune system to aberrant responses to subsequent 'delayed' infections.

Aims: To determine whether leukaemia (any leukaemia and ALL) diagnosed at age <20 years is associated with the following measures of population mixing at community level (Kinlen's hypothesis): 1) volume and diversity of incoming migrants into communities, and 2) change in annual in-migration; or with proxy measures of exposure to infections (Greaves' hypothesis): 3) birth order, 4) child density in the neighbourhood, and 5) extra-familial child-care.

Methods: The study uses data from the Swiss National Cohort (SNC), the Swiss Childhood Cancer Registry (SCCR), the Swiss cytogenetic database (SCD) and demographic data from the Swiss Federal Statistical Office. Primary outcomes are any leukaemia and ALL in particular. Secondary outcomes are the most prevalent immunophenotype, B-cell-precursor ALL, and cytogenetic subgroups like high hyperdiploidy and TEL-AML1 translocation. Main exposures are percentage of the population that moved into a community within the last 5 years, diversity of areas of origin (Shannon's entropy), change in annual volume of incoming migrants relative to average in previous years, the rank of the child among all live births of the same mother, neighbourhood indices of child density developed using road network connectivity, and parental full-time employment as a proxy measure of extra-familial child-care.

Rationale and Significance: The possibility that childhood leukaemia might be associated with a specific infection or with later exposure to infections is highly relevant for prevention. Previous studies were limited by the lack of spatial or temporal precision and few studies were able to use both residential locations at birth and at diagnosis. In the present study only routine databases with national coverage will be used and precise geocoding of the address at both birth and at diagnosis will allow high temporal and spatial resolution.

Current status of project: Analyses is ongoing and results for a first publication are currently being written up.

Study team: Spycher BD, Kuehni CE, Lupatsch JE, Kreis C. Institute of Social and Preventive Medicine, University of Bern.

Funding: Cancer Research Switzerland (Grant No KFS-3049-08-2012)

Contact: Ben Spycher (ben.spycher@ispm.unibe.ch)

4.13 The Spatial Epidemiology of Childhood Cancer in Switzerland

Background: Childhood cancer is a major cause of death in children but the associated risk factors are still largely unknown. Numerous environmental causes, such as background ionising radiation, air pollution, or electromagnetic fields have been suspected and infections in early life may also play a role. Many of these hypotheses imply a spatially heterogeneous distribution of cancer incidence, making them potentially testable with methods of spatial epidemiology. For instance, the putative effects of cosmic ionizing radiation could lead to detectable differences in incidence according to altitude, particularly in a mountainous country like Switzerland. Outbreaks of infections caused by a rapid influx of people into an isolated area could lead to clusters of cancer cases.

Aims: This study aims to investigate 1) whether the incidence of childhood cancer in Switzerland during the period 1985 to present was associated with natural ionizing radiation (cosmic, terrestrial, domestic radon) and traffic related air pollution, and whether there is an interaction between traffic related air pollution and domestic radon 2) whether the incidence of childhood cancer was elevated in communities that experienced rapid population influxes (population mixing) and 3) whether there is evidence for a general tendency of cases to cluster in space and in space and time.

Methods: This study includes the entire Swiss resident population aged <20 years. Data on cancer diagnoses in this population will be obtained from the SCCR and data on the population at risk from the SNC. Outcomes will be any childhood cancer and major diagnostic subgroups such as leukaemia, lymphomas, and tumours of the central nervous system. Among leukaemias, we will separately investigate acute lymphoblastic leukaemia (ALL), and important cytogenetic subtypes of ALL. Dose rates of outdoor cosmic and terrestrial ionising radiation at places of residence will be estimated from existing radiation maps and indoor radon gas concentrations using a previously developed prediction model. Proxy measures for traffic related air pollution will include distance of place of residence to near major roads, to nearest petrol stations or motor vehicle service stations, and predicted outdoor concentrations of specific pollutants.

Significance: The planned work will advance importantly our understanding of the role of environmental risk factors (or the lack thereof) in the aetiology of childhood cancer.

Current status of project: Analyses is ongoing.

Study team: Spycher BD, Kreis C, Kuehni CE, Institute of Social and Preventive Medicine, University of Bern.

Funding: Swiss National Science Foundation (Ambizione, Grant Nr. 147987)

Contact: Ben Spycher (ben.spycher@ispm.unibe.ch)

5. Publications

All articles published using SCCR data from January 2006 – December 2014 are reported below. Additional publications related to the SCCR or SPOG can be found on the SCCR and SPOG websites: www.childhoodcancerregistry.ch and www.spog.ch.

5.1 Publications in peer-reviewed journals

2014

published

Brown MC, Levitt GA, Frey E, Bardi E, Haupt R, Hjorth L, Kremer LC, Kuehni C, Lettner C, Mulder RL, Michel G, Skinner R on behalf of PanCareSurFup. The views of European clinicians on guidelines for long-term follow-up of childhood cancer survivors. Pediatr Blood Cancer. published online 2014.

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2013

Gianinazzi ME, Rueegg CS, Wengenroth L, Bergstraesser E, Rischewski J, Ammann RA, Kuehni CE, Michel G. Adolescent survivors of childhood cancer: are they vulnerable for psychological distress? Psycho-Oncology 2013; 22(9), 2051–2058

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6. Appendix: Classification of cancer diagnoses

International Classification of Childhood Cancer - ICCC-3

The third edition of the International Classification of Childhood Cancer (ICCC-3) represents the standard for presentation of international data on childhood cancer incidence and survival. It applies the rules, nomenclature and codes (morphology, topography and behaviour) of the ICD - O-3. ICCC-3 categories are defined in conformity with international classifications of the pathology and genetics of childhood cancers. In the ICCC-3, three hierarchical levels have been developed: level one consists of 12 main diagnostic groups and level two of 47 diagnostic subgroups. These two levels of the ICCC-3 allow standardised comparison of the broad categories of childhood tumours. Level three, an optional «extended» classification, comprises two to eleven divisions of selected diagnostic subgroups. The division of some diagnostic subgroups, e.g. leukaemia and Non-Hodgkin lymphomas, reflects the availability of detailed cytogenetic or molecular information that permits homogeneous groups of tumours to be distinguished within them and thus allows their separate study. The Swiss childhood cancer registry (SCCR) uses level one to three. Only malignant neoplasms are classified in ICCC-3, with the exception of non-malignant intracranial and intraspinal tumours. Tumours known to occur only rarely in young patients are also included in ICCC-3. The ICCC-3 is used if data are compared with other childhood cancer registries.

International Statistical Classification of Diseases for Oncology - ICD-O-3

The third edition of the International Statistical Classification of Diseases for Oncology (ICD-O-3) has been developed by a working group hosted by the International Association of Research in Cancer (IARC) and WHO. The morphology code for neoplasm has been revised, especially for lymphomas and leukaemia. In contrast to the International Classification of Diseases, 10th revision (ICD-10), ICD-O-3 uses only one set of four characters for topography (based on the malignant neoplasm section of ICD-10). The topography code remains the same for all neoplasms of that site. The behaviour code is incorporated as the fifth digit in the morphology field. It identifies whether the tumour is malignant, benign, of uncertain or unknown behaviour, in situ, presumed to be primary or secondary. For all tumours diagnosed since 1st January 2014 the SCCR uses the 2011 updates to ICD-O-3 which include new terms, codes and behaviour combinations. This allows e.g. B lymphoblastic leukaemias to be further classified according to their exact cytogenetic and molecular characteristics, which are relevant for disease prognosis. ICD-O-3 is used to compare data with general cancer registries.

International Statistical Classification of Diseases and Related Health Problems - ICD-10

The International Statistical Classification of Diseases and Related Health Problems (ICD) permits the systematic recording, analysis, interpretation and comparison of mortality and morbidity data collected in different regions and at different time periods. The ICD has become the international standard diagnostic classification for all general epidemiological purposes. The ICD-10 classification comprises three volumes: Volume 1 contains the main classifications; Volume 2 provides guidance for users of the ICD; and Volume 3 is the alphabetical index to the classification. Classification is divided into 21 chapters. The first character of the ICD code is a letter. Each letter is associated with a particular chapter, e.g. the letter D is used in both chapter II «Neoplasms» and chapter III «Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism». The topography code in Volume 3 describes the site and the behaviour of the neoplasm: malignant, secondary or metastatic, in situ, benign or of unknown behaviour. The morphology codes listed in Volume 1 are the same as those used in the special adaptation of the ICD for oncology, the ICD-O97.

Schweizer Kinderkrebsregister
Registre Suisse du Cancer de l'Enfant
Registro Svizzero dei Tumori Pediatrici
Swiss Childhood Cancer Registry

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