Original Research Article - Epidemiology

Space-time clustering of childhood cancers in Switzerland: A nationwide study

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Keywords

leukaemia; central nervous system tumours; soft tissue sarcoma; cancer registry; Europe

Abbreviations

ALL - acute lymphoid leukaemia

CNS - central nervous system

ICCC3 - International Classification of Childhood Cancers, Third Edition

SCCR - Swiss Childhood Cancer Registry

Novelty and Impact

This nationwide study found evidence of space-time clustering of childhood leukaemia around the time of birth but not at diagnosis nor for other diagnostic groups. The study is unique in that it corrects for uneven regional population shifts, a potential source of bias in earlier studies, at high geographic resolution. The small spatial (<1 km) and temporal (<2 years) scale of the clustering could indicate a leukaemogenic infection occurring around birth or *in utero*.

Abstract

The aetiology of childhood cancers remains largely unknown. It has been hypothesized that infections may be involved and that mini-epidemics thereof could result in space-time clustering of incident cases. Most previous studies support spatio-temporal clustering for leukaemia, while results for other diagnostic groups remain mixed. Few studies have corrected for uneven regional population shifts which can lead to spurious detection of clustering. We examined whether there is space-time clustering of childhood cancers in Switzerland identifying cases diagnosed in children aged <16 years between 1985 and 2010 from the Swiss Childhood Cancer Registry. Knox tests were performed on geocoded residence at birth and diagnosis separately for leukaemia, acute lymphoid leukaemia (ALL), lymphomas, tumours of the central nervous system, neuroblastomas and soft tissue sarcomas. We used Baker's Max statistic to correct for multiple testing and randomly sampled time-, sex- and age-matched controls from the resident population to correct for uneven regional population shifts. We observed space-time clustering of childhood leukaemia at birth (Baker's max P = 0.045) but not at diagnosis (P = 0.98). Clustering was strongest for a spatial lag of <1 km and a temporal lag of <2 years (Observed/expected close pairs: 124/98; P Knox test = 0.003). A similar clustering pattern was observed for ALL though overall evidence was weaker (Baker's max at birth P = 0.13). Little evidence of clustering was found for other diagnostic groups (P>0.2). Our study suggests that childhood leukaemia tends to cluster in space-time due to an etiologic factor present in early life.

Introduction

The aetiology of most childhood cancers remains currently unknown. In developed countries, the most frequent diagnostic groups are leukaemia, predominantly acute lymphoid leukaemia (ALL), and tumours of the central nervous system (CNS). With the exception of ionizing radiation,[1] no environmental risk factors for these cancers have been established.[2, 3] Several infectious agents are known to cause cancer in humans though.[4] Among paediatric cancers, Burkitt lymphoma and Hodgkin lymphoma are linked with Epstein-Barr virus.[4] An infectious aetiology has also been proposed for childhood leukaemia.[5] The observation of spatial clusters of childhood leukaemia cases has led to the suggestion that a specific infection is involved in aetiology.[6] If specific infectious agents cause cancer in children, incident cases might show a tendency to cluster in space and time, i.e. to appear more frequently close in time and space to each other than if they occur independently and the risk of disease is spread evenly across the study area. Such space-time clustering would best be detectable from residential locations of cases at the time of infection, not necessarily at the time of diagnosis when children may have relocated. Investigation of the space-time pattern both at birth and at diagnosis may thus help uncover the presence and timing of a potentially causative infection.[7]

Since the early 1960s numerous studies have investigated space-time clustering of childhood leukaemia (studies up to 2004 were reviewed by McNally and Eden[8] and Little[9]). The majority of these studies found evidence of space-time clustering around the time of diagnosis,[10-18] birth[19-21] or both.[22, 23] Space-time clustering was most pronounced for small spatial and temporal lags of a few kilometres and a few months respectively. Studies that did not find evidence of space-time clustering typically either had small study samples[24, 25] or used relatively large spatial units of analysis such as municipalities or bigger administrative areas in search of local clusters.[26, 27] Separate analyses around diagnosis by age group suggest

that space-time clustering is relatively more apparent in younger children (≤5 years) than in older ones.[10, 11, 13, 15, 17]

A number of studies have reported space-time clustering for other major diagnostic groups of childhood cancer including tumours of the central nervous system[7, 28, 29] and lymphoma[7, 18, 22, 30] but the evidence is more mixed. A notable exception is Burkitt lymphoma for which a majority of studies found a positive association.[31-33]

Assessing space-time clustering poses some methodological challenges, however. Statistical tests are typically based on data from cases only, and uneven shifts in the underlying population are liable to bias results. Rapid population growth in certain areas but not in others can mimic the effects of spatio-temporal clusters by increasing the number of cases in the former, even though incidence rates remain constant throughout space and time, leading to erroneous conclusions about a clustering effect.[34] Few studies have attempted to correct for this[13, 35] and none could consider population shifts at a very small geographic scale. In addition, spatial resolution in most studies was low; only a handful of studies were based on exact geocodes of children's residential location.[15, 36-38] This problem was mitigated to some extent though for studies, notably from the U.K., using small area units. Moreover, even though space-time clustering analyses were commonly performed for different space-time lags and diagnostic groups, few studies explicitly corrected for multiple testing;[12, 20, 35] the majority of recent studies bypassed this problem by using spatio-temporal K-functions to test for evidence of space-time clustering.[7, 10, 11, 21]

In the current study, we investigated the presence of space-time clustering of childhood cancers in Switzerland using precise residential locations. We focused on the major diagnostic groups, namely leukaemia, ALL, CNS tumours, neuroblastomas and soft tissue sarcomas. Cases were identified from the Swiss Childhood Cancer Registry for the period 1985-2010. We paid special attention to correct for uneven population growth over the study period by

sampling representative control locations using a combination of census data and small-area population statistics. Exact geocodes of the residential locations were available for the entire population at census and at the time of birth and diagnosis for cases. We also corrected for multiple testing.

Material and Methods

Population

The study population included cancer cases from the Swiss Childhood Cancer Registry (SCCR) diagnosed at age <16 years between January 1, 1985 and December 31, 2010. Children were required to be living in Switzerland at diagnosis. The SCCR is a nationwide population-based registry with an estimated coverage of 91% of cancers diagnosed in Switzerland over this period.[39] Since 1995 completeness has been about 95%. From the SCCR, we obtained residential address at diagnosis and, for children born in Switzerland, address at birth. Addresses were geocoded to the Swissgrid coordinate system through linkage with the database of geo-referenced street addresses maintained by Swiss Post (GeoPost) or manually using the geoportal of the Swiss Federal Office of Topography (www.geo.admin.ch). Precise geocodes to within 50 m were obtained for 94% of available residential addresses. The margin of error was <100 m for another 5% while the exact location remained uncertain for the remaining less than 1% of addresses. We investigated pairs of cancer cases with coordinates at birth or diagnosis <50 m apart for possible sibling relationships using patient record data and retained only one record from identified sibling pairs.

In order to correct the analyses for uneven population growth, data on the resident population were obtained for the study period 1985-2010. Geocoded residence, municipality of residence, age and sex were available for the entire resident population at the time of the

Swiss national censuses in 1990, 2000 and 2010 from the Swiss National Cohort study.[40] Population counts by age, sex and municipality were also obtained for the 1980 census. Annual data on the total population and number of live births by municipality and sex were gathered from the Swiss Federal Office of Statistics.

Outcomes

We investigated space-time clustering separately for the following six diagnostic groups according to the International Classification of Childhood Cancers, Third Edition[41] (ICCC3): leukaemia (diagnostic group I), ALL (I.a), lymphomas (II), tumours of the central nervous system (CNS) (III), neuroblastomas (IV) and soft tissue sarcomas (IX). For leukaemia and ALL we additionally performed clustering analysis for children aged 0-4 and 5-15 years old at diagnosis. These groupings were selected because the number of available cases exceeded our *a priori* chosen threshold of 300.

Sampling of control locations

In order to account for uneven population shifts, we sampled control locations representing the geographic distribution of the general population at the time of cases' birth and diagnosis, respectively. To achieve this, we randomly sampled 999 control locations for each case using a two-stage approach: First, municipalities were randomly sampled with replacement, with each municipality weighted by the number of age group (0-4, 5-9 and 10-15 years) and sex peers residing in that municipality in the case's year of birth or diagnosis, respectively. For the analysis around the time of birth, sampling weights were derived from the number of male and female live births. For the analysis around the time of diagnosis, age group and sex specific population proportions were computed for every municipality for census years (1980, 1990, 2000, 2010), and linearly interpolated for the years in-between. Sampling weights were then obtained by applying these proportions to annual total population in each municipality. At the second stage, residential locations were randomly sampled from the census data (1990,

2000 and 2010) among age group and sex peers living in the municipalities selected during the first stage. For this we probabilistically selected one of the two censuses closest to the cases' year of birth (or diagnosis). If, for example, a child was born (diagnosed) in 1996, a control location was sampled with probability 0.4 and 0.6 from the 1990 and 2000 census, respectively.

Over the study period, mergers and territorial swaps between municipalities were common. For the sampling process, we merged neighbouring modified municipalities to ensure that they had consistent geographical boundaries throughout the study period.

Statistical analyses

Space-time clustering was analysed separately at the time of birth and diagnosis using an unbiased version of the Knox test[42] as proposed by Kulldorff and Hjalmars[34] to adjust for uneven regional population shifts. The Knox test statistic counts the number of close pairs of cases that occur within a pre-specified spatial and temporal lag of each other. We chose as critical values spatial lags of 0.5, 1, 2, 5 and 10 km and temporal lags of 0.5, 1, 1.5 and 2 years *a priori* in accordance with previous studies. The spatial lag between two cases was calculated as the Euclidean distance between residential coordinates.

We standardized the counts of close pairs using empirical expected values and standard errors as proposed by Barton and David [43] (Standardized counts are referred to here as z-values). A null distribution for z-values was obtained by calculating z-values for each of the 999 datasets of sampled control locations accordingly. We calculated the p-value as the number of z-values thus obtained that exceeded the empirical z-value divided by 1000. To account for multiple testing inherent in computing p-values for all combinations of spatial and temporal lags, we used Baker's Max[44] method. Under this approach, only the maximum z-value over all combinations of spatial and temporal lags was considered. Baker's max p-value equals the

fraction of maximum z-values of the random samples that exceed the maximum z-value for the empirical data set.

In order to assess the extent of potential bias due to population shifts, we repeated the analyses with the standard approach whereby the null distribution is obtained by random permutation of case locations.[45] All computations were performed using the R language for statistical computing. Knox tests were computed using an adapted code originally provided by Tango.[46]

Results

Study population

In total 3,795 cases were eligible in the SCCR data base for analysis. After excluding those with missing geocodes and sibling cases, we included 1,485 cases with leukaemia, 996 with CNS tumours and 635 with lymphomas in the analysis of space-time clustering at the time of diagnosis (Figure 1). After additionally excluding children born before 1985, born abroad or with uncertain country of birth, corresponding numbers included in analyses at the time of birth were 1,052, 689 and 353 respectively. Table 1 indicates the number of cases by diagnostic group, age group and gender included in the analysis.

The frequency distributions of the six diagnostic groups by age group and sex categories reflect known incidence patterns. The frequencies of the subtypes of leukaemia are typical for industrialised countries: of the 1,052 cases included in the analysis around birth, 852 were of type ALL and 147 were acute myeloid leukaemias (AML). Among the cases of ALL, 731 were of the precursor B-cell subtype or 'common ALL' (cALL) and 88 were of the precursor T-cell subtype with the remainder being either unspecified precursor cell leukaemias or Burkitt-cell leukaemias. Cases of ALL show the characteristic childhood peak with 447 being diagnosed in children aged 2-5 years, of which 89% were of the precursor B-cell subtype.

Space-time clustering

Results of tests for space-time clustering adjusted for multiple testing over different spatial and temporal lags are shown in Table 2. For leukaemia, we found evidence of space-time clustering around the time of birth (P = 0.045) but not around diagnosis (P = 0.984~~1~~). By contrast, we found no evidence of space-time clustering for lymphomas and tumours of the central nervous system, neither around birth nor around diagnosis (P>0.5). Detailed results from individual Knox tests for the different diagnostic groups are shown in Tables 3-4 and Figure 2 and in the supplementary Tables S1-S18 and Figure S1.

For leukaemia, evidence of space time-clustering around birth was strongest for spatial lags of <1 km and <2 km combined with temporal lags of <1.5 and <2 years (Table 3). For comparability across different lags and diagnostic groups, the results of the Knox tests are reported in Figure 2 as standardized numbers of close pairs (z-values) and as absolute numbers of close pairs in excess of the numbers expected. There were 124 pairs of children with leukaemia who were born <1 km and <2 years apart, 27% more than the 98 expected (P = 0.003; Table 3, Figure 2). Similar effect sizes were observed for leukaemia in children aged 0-4 years old; there were 19% more close pairs than expected among children born <1 km and <2 years apart (P = 0.13; Table 4). The clustering effect for the same spatial and temporal lags was considerably weaker for children aged 5-15 years old (10% more close pairs than expected, P = 0.30, Supplementary Table S1).

For ALL, although not statistically significant after adjustment for multiple tests (Table 2), we observed an almost identical pattern of space-time clustering at birth, which is not surprising as the large majority of leukaemia cases had ALL (Table 1). A 27% excess of close pairs was observed for the lags of <1 km and <2 years (P < 0.013; Supplementary Table S2). As with leukaemia, there was no evidence of space-time clustering around the place and time of diagnosis (Table 2).

Some indications from individual Knox tests of possible space-time clustering of cancers other than leukaemia are noteworthy, although not statistically significant after correcting for multiple testing (Table 2): For neuroblastomas around time of birth and lags <10 km and <2 years, there were 182 observed close pairs compared to 156 expected, an excess of 16% (P = 0.019; Supplementary Table S7, Figure 2). For soft tissue sarcomas around time of birth and lags <5 km and <2 years, 51 instead of 39 expected close pairs were observed, an excess of 31% (P = 0.027; Supplementary Table S8, Figure 2).

There was little difference between the results with or without adjustment for uneven regional population shifts: Whether the null distribution was computed by random permutation of case locations or by random sampling of control locations from the general population resulted in almost identical p-values of individual Knox tests. For leukaemia around the time of birth and lags <1 km and <2 years, these P-values were 0.004 and 0.003, respectively.

Discussion

Summary of results

In this nationwide study, which paid special attention to avoiding confounding by uneven population growth, we found evidence of space-time clustering of childhood leukaemia around the place and time of birth. Evidence was strongest for clustering at a small spatial lag of <1 km and a temporal lag of <2 years. The same pattern was observed for ALL. By contrast, there was no evidence of space-time clustering of childhood leukaemia around diagnosis. We also found little evidence of space-time clustering for lymphomas and tumours of the central nervous system. There were, however, indications of space-time clustering of neuroblastomas (<10 km; <2 years) and soft tissue sarcomas (<5 km; <2 years) around birth that did not reach conventional significance levels after adjusting for multiple testing.

Discussion of results in the context of earlier studies

Our findings agree with most previous studies investigating space time clustering of leukaemia at birth.[20-22] As in these studies, we found the effect of space-time clustering was most pronounced for short spatial lags of 1-2 kilometres, whereas the corresponding temporal lag of <2 years in our study was slightly longer than the critical values observed elsewhere. Studies using large samples generally found evidence of space-time clustering of leukaemia cases at birth, with one notable exception[7] that used as distance metric for the space-time clustering analysis distance to cases' nearest neighbours (which varies with population density) rather than a fixed distance threshold.

The lack of space-time clustering of leukaemia at diagnosis in our analysis stands in contrast to findings from previous studies, a majority of which were positive.[11, 15, 22] However, our results concur with three mid-sized studies looking at incident cases of ALL which also found evidence of space-time clustering at birth but not at diagnosis.[19-21] Still, studies with large samples typically detected a clustering effect at diagnosis.[13, 30] Two recent large studies that found no effect were looking for local clusters relying on relatively large units of analysis.[26, 27] In our analysis, the lack of significant evidence does not imply absence of any space-time clustering at diagnosis though. For children aged 0-4 years old, the effect sizes for spatial lags <2 km and temporal lags of <2 years indicate an excess of pairs close in space and time, even if no individual Knox test is below the conventional 5%-level of significance.

Similar to our results, a number of previous studies did not find evidence of space-time clustering of lymphoma or CNS tumours.[11, 20, 35] McNally et al.[11] found no evidence of clustering at diagnosis for either, even though their study sample (n = 32'295) was presumably large enough and spatial resolution high enough to detect any important effect. By contrast, some studies have reported space-time clustering for these diagnostic groups.[7, 28, 30] McNally

et al.[7] found evidence of strong clustering of Hodgkin lymphomas and moderate clustering of CNS tumours at birth.

Few studies have investigated space-time clustering of neuroblastomas and soft tissue sarcomas. McNally et al.[47] found no significant clustering effect for neuroblastomas neither at birth nor at diagnosis. McNally et al. found evidence of space-time clustering for soft tissue sarcomas at diagnosis at spatial and temporal lags similar to our results,[11] but no effect around birth.[7]

Strengths and weaknesses

Notwithstanding this being a nationwide study, statistical power may have been too low for some of the investigated diagnostic groups to detect space-time clustering. Though coverage of the SCCR is high, our study could not include all cancer cases that actually occurred. An under ascertainment of cases might have diluted the observed tendency for clustering. Some cases were also lost to analyses due to missing geocodes. Moreover, for our adjustment for uneven population shifts precise locations of residence were known for the entire population only at census time points. Thus our sampling of control locations may have been imperfect - although it did account for annual population fluctuations at the municipal level.

The major strength of our study was the availability of precise geocodes for place of residence for both cases and the entire child population. This not only allowed us to investigate space-time clustering at small spatial scales but also made it possible to adjust for potential bias due to uneven population growth. To our knowledge, no previous study of childhood cancers has applied this methodology at such high spatial resolution; Hjalmars et al.[35] had to rely on parishes as units of analysis. Other studies of space-time clustering either used similarly large units of analysis[13] or - if geocodes for residential addresses were available - resorted to interrupting the study period in an effort to reduce bias due to uneven population shifts.[18, 22] In our study, the results from the adjusted analyses differed little from those following the

standard approach of random permutation of case locations – which cannot capture uneven regional population shifts - suggesting that such a bias, if present, was small. This finding is noteworthy given the long study period of 26 years and suggests that bias from uneven population shifts can probably be excluded for the current analysis and raises confidence in results from other studies that could not account for this at all. Moreover, we took further steps to reduce the risk of producing spurious evidence of space-time clustering by adjusting for multiple testing.

Interpretation and conclusions

The space-time clustering of childhood leukaemia around the time of birth observed in the present study thus appears to be real rather than a spurious effect of uneven population growth. The finding is also supported by a majority of other studies. This suggests that a substantial number of close pairs of leukaemia cases (as many as exceed chance) are likely to share etiological factors that clustered temporally in their neighbourhood. The small spatial scale of the clustering could be indicative of an infection.

Evidence of space-time clustering was strongest for a temporal lag of two years, which is a relatively long time period considering that local epidemics can be short lived. However, while this finding would be compatible with an extended period of locally increased exposure to a risk factor e.g. a longer lasting epidemic or environmental hazard, it is also compatible with a short-lived increase in exposure combined with an extended age window of susceptibility. The observed pattern of clustering might for instance occur if children aged 0-2 years were susceptible to the leukaemogenic effects of an infection that tends to come about as short and highly localised mini-epidemics.

The results of the current study thus give further credence to the hypothesis that an infectious agent might be involved in the aetiology of childhood leukaemia. Several hypotheses regarding a possible role of infections have been proposed. Kinlen[6] conjectured that childhood

leukaemia is a rare response to a common, yet unidentified subclinical infection. Kinlen[6] suggested that situations of 'population mixing' – large-scale influxes of urban migrants into previously isolated rural communities – could result in localised epidemics and a subsequent increase in childhood leukaemia rates. Greaves,[5] seeking to explain the peak incidence of the precursor B-cell type or 'common' ALL at ages 2-5 years, speculated that the lack of exposure to common early childhood infections in modern, 'hygienic' societies might render the immune system prone to a pathological response to later, 'delayed' infections. Greaves[5] posited a 'two-hits' model in which a first hit occurring *in utero* induces chromosomal changes in a precursor B-cell that is passed on to daughter cells while infections were hypothesized to play a crucial role in the second hit prompting the onset of overt leukaemia. Smith[48] proposed that the childhood peak in ALL characteristic of more affluent societies might be due to an infection that occurred *in utero*.

The evidence in our analysis of space-time interaction around the place and time of birth but not around the place and time of diagnosis suggests that such an infection would have to occur *in utero* – as suggested by Smith[48] – or in early life. Smith[48] named as a candidate infectious agent the JC virus of the polyomavirus family. However, studies searching for viral genomes, including JC virus, in ALL cells or in neonatal blood spots have consistently reported negative results.[49, 50] Stratification of our analyses by age at diagnosis (0-4, 5-15 years) reduced the measured effect sizes, suggesting that cases implicated in clustering were born close to each other in time but diagnosed at widely differing ages. We therefore speculate that an infectious agent could be involved in early disease initiating events, and that these events are followed by protracted and variable latent periods or require secondary events for disease onset. Greaves'[5] 'two-hits' model posited no particular environmental stimuli for the first hit occurring *in utero* and these could in principle include infections and thus provide a possible explanation for the pattern of space-time clustering observed in our analysis. However, Greaves[5] assumed infections to play a crucial role in the second postnatal hit yet in

our analysis cases of ALL aged 0-4 years old at the time of diagnosis showed an overhang of close pairs but no evidence of space-time interaction at conventional significance levels (Supplementary Table S13). Kinlen's hypothesis is a less plausible explanation for our finding of spatio-temporal clustering at birth as the critical time point for infection is assumed to be closer to the time of diagnosis.[6, 51] However, Kinlen refers to a very particular migratory pattern, so the absence of significant space-time clustering around the time of diagnosis in this nationwide study cannot be taken as evidence against his population mixing hypothesis.

Our analyses provide few clues with regard to differences in aetiology between the subtypes of leukaemia. We ran separate analyses of ALL as it represents a large and relatively homogenous subgroup but because of the small sample sizes we did not consider subgroups such as cALL or specific cytogenetic subtypes. While it is possible that the observed space-time clustering is driven by one or a few subtypes, the fact that effects sizes for ALL were similar to those for all subtypes of leukaemia combined may indicate that the two broad subgroups AML and ALL and perhaps the smaller subdivisions are similarly affected.

The lack of significant evidence for the other major diagnostic groups does not necessarily mean absence of space-time clustering. Our analyses may have lacked the statistical power needed to detect effects of clustering for these groups while correcting for multiple testing. The effect sizes of the Knox tests of neuroblastomas and soft tissue sarcomas, which were comparable to those for leukaemia/ALL, indeed suggest that this may be the case. Alternatively, if indeed there is space-time clustering around birth and few children migrate between birth and diagnosis, the peak incidence of leukaemia at 2-5 years of age could induce a weaker, time-shifted clustering pattern at diagnosis which may be detectable in large studies only. In our study 34% of leukaemia cases moved house between birth and diagnosis. Unfortunately migration pattern were almost never reported by other investigators, with the

exception of Birch et al.[10] who reported a slightly higher rate. Birch et al.[10] found evidence of space-time clustering around place and time of diagnosis but not around birth.

The presence of space-time clustering also does not necessarily imply infections but could point to other localized hazards present for a limited period of time. What the current study did not analyse is the presence of purely spatial clustering, which could be triggered by a more permanent local environmental hazard. The Knox test is insensitive to localized hazards leading to continuously elevated risks.

In conclusion, our study suggests that children who develop leukaemia show a tendency to cluster in time and space at birth and that this tendency is not explained by regional population shifts. The prima facie evidence of the observed space-time clustering pattern suggests that an infectious agent is involved in aetiology but further research is necessary to assess the potential influence of environmental risk factors.

Acknowledgements

This study was supported by Swiss Cancer Research (# 3049-08-2012, # 3515-08-2014), the Swiss Federal Office of Public Health (# 08.001616, #10.002946, # 12.008357) and the Swiss Cancer League (#02224-03-2008). B.D. Spycher was supported by a Swiss National Science Foundation fellowship (PZ00P3_147987).

The work of the Swiss Childhood Cancer Registry is supported by the Swiss Paediatric Oncology Group (www.spog.ch), Schweizerische Konferenz der kantonalen Gesundheitsdirektorinnen und –direktoren (www.gdk-cds.ch), Swiss Cancer Research (www.krebsforschung.ch), Kinderkrebshilfe Schweiz (www.kinderkrebshilfe.ch), the Federal Office of Health (FOH) and the National Institute of Cancer Epidemiology and Registration (www.nicer.ch).

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Conflict of interest

The authors declare that they have no conflict of interest.

Ethical standard

Ethics approval was granted through the Ethics Committee of the Canton of Bern to the SCCR.

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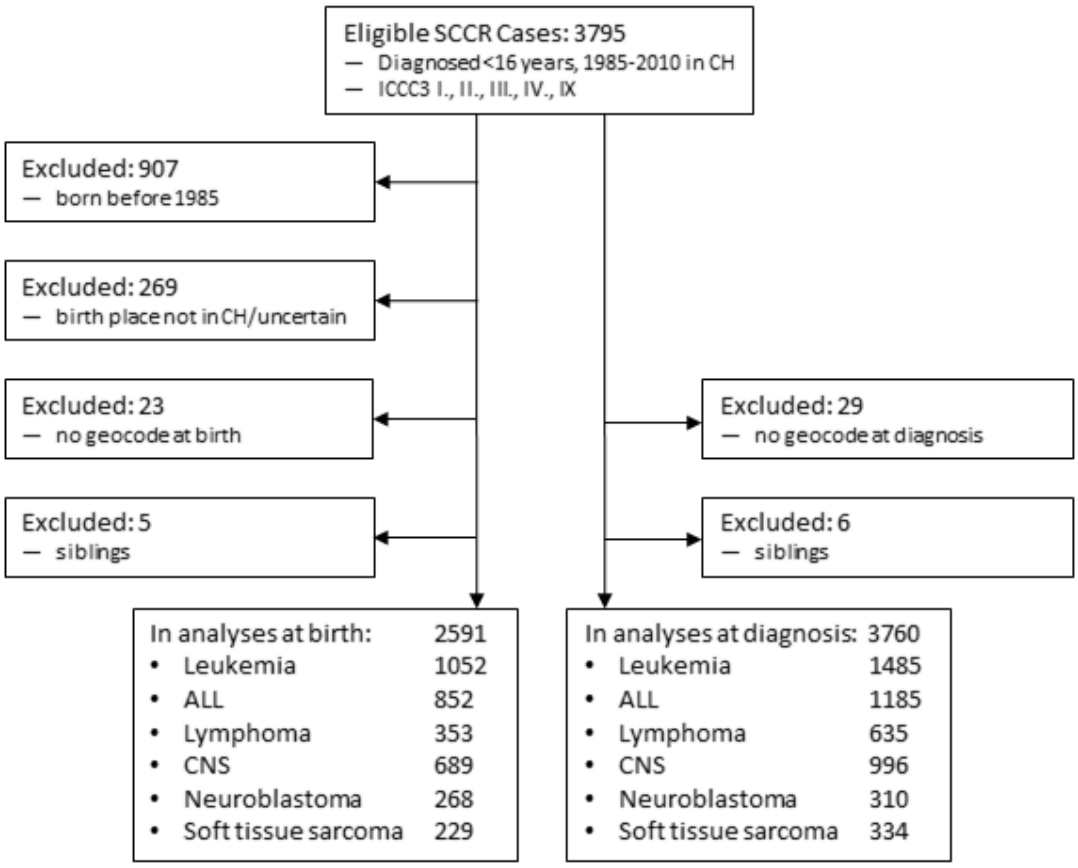
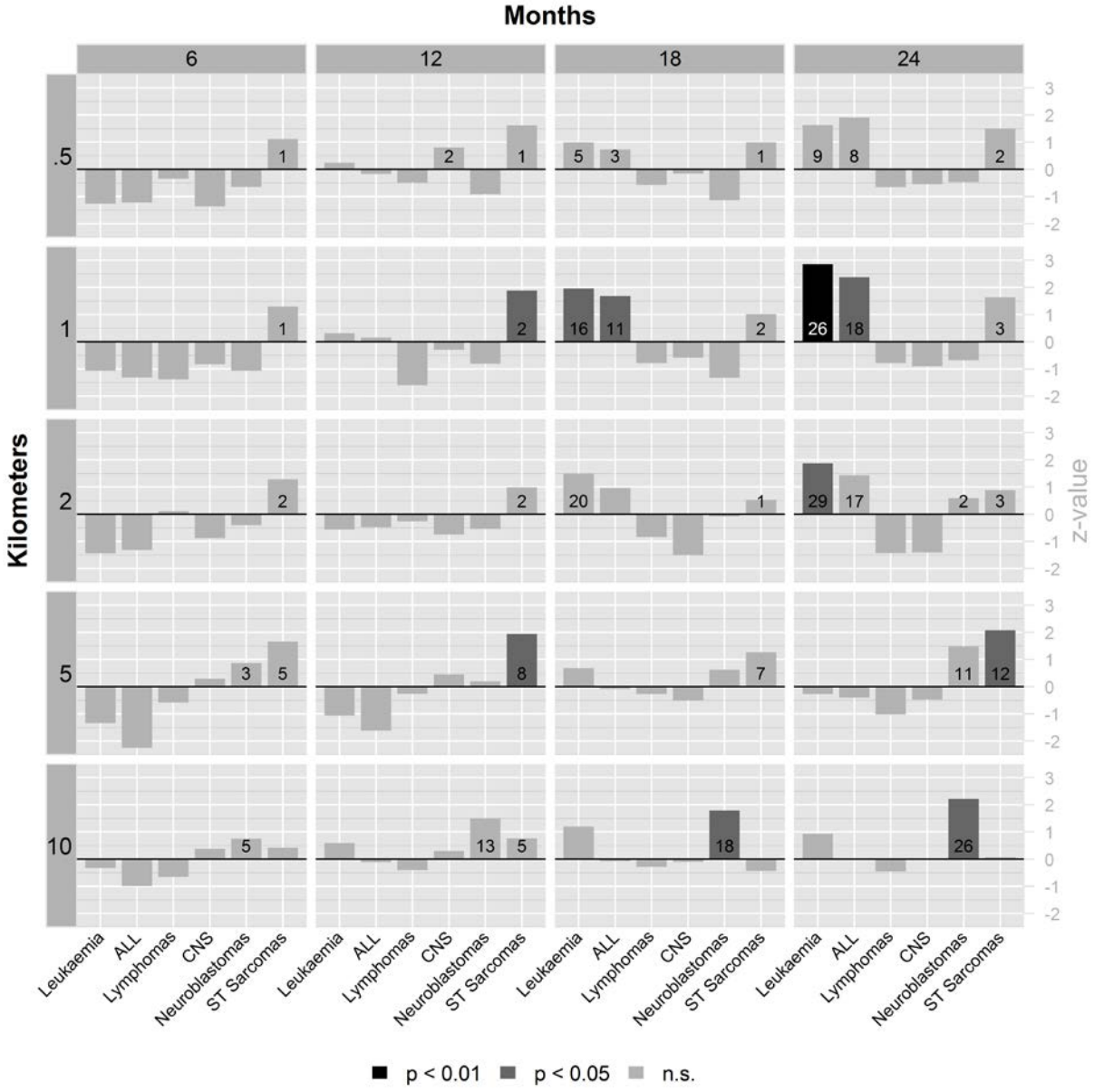
Figure legends

Fig. 1 Flow chart of study population

Fig. 2 Standardized numbers of close pairs of cases in excess of expected numbers (z-values) for different diagnostic groups for all combinations of spatial and temporal lags around the place and time of birth. Figures at the bottom of the bars indicate absolute numbers of excess close pairs


Eligible SCCR Cases: 3795
— Diagnosed <16 years, 1985-2010 in CH
— ICCC3 I., II., III., IV., IX
Excluded: 907
— born before 1985
Excluded: 269
— birth place not in CH/uncertain
Excluded: 23
— no geocode at birth
Excluded: 5
— siblings
Excluded: 29
— no geocode at diagnosis
Excluded: 6
— siblings
In analyses at birth: 2591
• Leukemia 1052
• ALL 852
• Lymphoma 353
• CNS 689
• Neuroblastoma 268
• Soft tissue sarcoma 229
In analyses at diagnosis: 3760
• Leukemia 1485
• ALL 1185
• Lymphoma 635
• CNS 996
• Neuroblastoma 310
• Soft tissue sarcoma 334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Leukaemia
ALL
Lymphomas
CNS
Neuroblastomas
ST Sarcomas
p < 0.01
p < 0.05
n.s.

Supplementary material

Space-time clustering of childhood cancers in Switzerland: A nationwide study

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Table S1 Results of Knox tests of cases of leukaemia at place and time of birth of children aged 5-15 years old

		Months			
		6	**12**	**18**	**24**
0.5 km	*Obs./Exp.*	0/1.6	2/3.2	3/4.7	6/6.2
	Ratio	0.00	0.63	0.64	0.97
	p-value	0.928	0.759	0.823	0.570
1 km	*Obs./Exp.*	4/4.7	12/9.2	15/13.7	20/18.1
	Ratio	0.85	1.30	1.09	1.10
	p-value	0.588	0.162	0.355	0.304
2 km	*Obs./Exp.*	8/12.0	24/23.6	37/35.1	48/46.3
	Ratio	0.67	1.02	1.05	1.04
	p-value	0.889	0.462	0.359	0.381
5 km	*Obs./Exp.*	40/43.4	84/85.2	134/126.6	166/167.0
	Ratio	0.92	0.99	1.06	0.99
	p-value	0.690	0.509	0.224	0.500
10 km	*Obs./Exp.*	103/110.5	218/216.8	337/322.3	431/425.1
	Ratio	0.93	1.01	1.05	1.01
	p-value	0.780	0.455	0.207	0.369

Table S2 Results of Knox tests of cases of acute lymphoid leukaemia at place and time of birth of children aged 0-15 years old

		Months			
		6	**12**	**18**	**24**
0.5 km	*Obs./Exp.*	3/5.9	11/11.5	20/17.2	31/22.7
	Ratio	0.51	0.95	1.17	1.37
	p-value	0.927	0.623	0.296	0.059
1 km	*Obs./Exp.*	12/17.4	35/34.1	62/50.7	85/67.1
	Ratio	0.69	1.03	1.22	1.27
	p-value	0.919	0.449	0.047	0.013
2 km	*Obs./Exp.*	34/42.4	79/83.2	134/123.7	181/163.7
	Ratio	0.80	0.95	1.08	1.11
	p-value	0.911	0.675	0.155	0.066
5 km	*Obs./Exp.*	128/155.8	278/305.8	453/454.8	592/601.7
	Ratio	0.82	0.91	1.00	0.98
	p-value	0.984	0.930	0.479	0.578
10 km	*Obs./Exp.*	354/373.0	729/732.0	1086/1088.5	1440/1440.1
	Ratio	0.95	1.00	1.00	1.00
	p-value	0.833	0.503	0.459	0.410

Table S3 Results of Knox tests of cases of acute lymphoid leukaemia at place and time of birth of children aged 0-4 years old

		Months			
		6	**12**	**18**	**24**
0.5 km	*Obs./Exp.*	1/2.4	4/4.6	5/6.8	9/9.0
	Ratio	0.43	0.87	0.74	1.00
	p-value	0.856	0.646	0.797	0.573
1 km	*Obs./Exp.*	3/6.2	10/12.1	20/17.9	27/23.6
	Ratio	0.49	0.83	1.12	1.14
	p-value	0.934	0.757	0.327	0.258
2 km	*Obs./Exp.*	12/15.6	25/30.4	47/45.1	61/59.5
	Ratio	0.77	0.82	1.04	1.03
	p-value	0.816	0.859	0.383	0.416
5 km	*Obs./Exp.*	45/60.2	94/117.3	169/174.0	221/229.7
	Ratio	0.75	0.80	0.97	0.96
	p-value	0.981	0.986	0.652	0.718
10 km	*Obs./Exp.*	135/137.1	256/267.3	393/396.7	515/523.5
	Ratio	0.98	0.96	0.99	0.98
	p-value	0.577	0.744	0.578	0.641

Table S4 Results of Knox tests of cases of acute lymphoid leukaemia at place and time of birth of children aged 5-15 years old

		Months			
		6	**12**	**18**	**24**
0.5 km	*Obs./Exp.*	0/1.1	1/2.3	2/3.4	5/4.5
	Ratio	0.00	0.44	0.60	1.12
	p-value	0.912	0.828	0.822	0.397
1 km	*Obs./Exp.*	2/3.2	7/6.3	9/9.4	13/12.5
	Ratio	0.62	1.10	0.95	1.04
	p-value	0.759	0.406	0.586	0.449
2 km	*Obs./Exp.*	5/7.2	16/14.1	23/21.0	30/27.8
	Ratio	0.70	1.14	1.10	1.08
	p-value	0.799	0.299	0.302	0.303
5 km	*Obs./Exp.*	19/24.5	47/48.2	76/71.7	95/95.0
	Ratio	0.78	0.98	1.06	1.00
	p-value	0.885	0.568	0.304	0.504
10 km	*Obs./Exp.*	60/65.0	127/127.9	195/190.3	251/252.1
	Ratio	0.92	0.99	1.02	1.00
	p-value	0.777	0.618	0.393	0.550

Table S5 Results of Knox tests of cases of tumors of the central nervous system at place and time of birth of children aged 0-15 years old

		Months			
		6	**12**	**18**	**24**
0.5 km	*Obs./Exp.*	1/3.5	9/6.9	10/10.5	12/13.8
	Ratio	0.29	1.29	0.96	0.87
	p-value	0.943	0.229	0.583	0.756
1 km	*Obs./Exp.*	8/10.6	20/21.3	29/32.1	37/42.4
	Ratio	0.75	0.94	0.90	0.87
	p-value	0.828	0.621	0.714	0.826
2 km	*Obs./Exp.*	25/29.7	54/59.6	76/89.7	104/118.6
	Ratio	0.84	0.91	0.85	0.88
	p-value	0.819	0.773	0.934	0.920
5 km	*Obs./Exp.*	112/108.9	225/218.2	319/328.4	424/434.3
	Ratio	1.03	1.03	0.97	0.98
	p-value	0.385	0.318	0.674	0.674
10 km	*Obs./Exp.*	259/253.0	514/507.0	760/762.9	1009/1008.9
	Ratio	1.02	1.01	1.00	1.00
	p-value	0.374	0.374	0.505	0.463

Table S6 Results of Knox tests of cases of lymphomas at place and time of birth of children aged 0-15 years old

		Months			
		6	**12**	**18**	**24**
0.5 km	*Obs./Exp.*	1/1.4	2/2.8	3/4.1	4/5.4
	Ratio	0.72	0.73	0.74	0.75
	p-value	0.635	0.665	0.708	0.759
1 km	*Obs./Exp.*	1/3.5	3/7.0	8/10.3	11/13.6
	Ratio	0.28	0.43	0.77	0.81
	p-value	0.939	0.958	0.788	0.773
2 km	*Obs./Exp.*	10/9.6	18/19.1	24/28.2	29/37.0
	Ratio	1.04	0.94	0.85	0.78
	p-value	0.441	0.605	0.802	0.920
5 km	*Obs./Exp.*	30/33.3	64/66.1	95/97.5	117/128.2
	Ratio	0.90	0.97	0.97	0.91
	p-value	0.695	0.600	0.586	0.854
10 km	*Obs./Exp.*	71/76.6	147/151.9	220/224.1	287/294.7
	Ratio	0.93	0.97	0.98	0.97
	p-value	0.753	0.676	0.608	0.677

Table S7 Results of Knox tests of cases of neuroblastomas at place and time of birth of children aged 0-15 years old

		Months			
		6	**12**	**18**	**24**
0.5 km	*Obs./Exp.*	0/0.4	0/0.8	0/1.2	1/1.5
	Ratio	0.00	0.00	0.00	0.65
	p-value	0.568	0.758	0.875	0.699
1 km	*Obs./Exp.*	0/1.1	1/2.1	1/3.2	3/4.3
	Ratio	0.00	0.47	0.31	0.70
	p-value	0.808	0.804	0.919	0.759
2 km	*Obs./Exp.*	3/3.8	6/7.4	11/11.2	17/14.9
	Ratio	0.80	0.81	0.98	1.14
	p-value	0.640	0.694	0.528	0.269
5 km	*Obs./Exp.*	18/14.8	30/29.0	48/44.1	69/58.5
	Ratio	1.22	1.03	1.09	1.18
	p-value	0.186	0.412	0.255	0.081
10 km	*Obs./Exp.*	44/39.4	90/77.5	136/117.8	182/156.3
	Ratio	1.12	1.16	1.15	1.16
	p-value	0.197	0.068	0.048	0.019

Table S8 Results of Knox tests of cases of soft tissue sarcomas at place and time of birth of children aged 0-15 years old

		Months			
		6	**12**	**18**	**24**
0.5 km	*Obs./Exp.*	1/0.4	2/0.7	2/1.1	3/1.4
	Ratio	2.84	2.84	1.90	2.16
	p-value	0.145	0.081	0.174	0.079
1 km	*Obs./Exp.*	2/0.8	4/1.7	4/2.5	6/3.3
	Ratio	2.39	2.39	1.60	1.82
	p-value	0.106	0.049	0.145	0.065
2 km	*Obs./Exp.*	5/2.9	8/5.7	10/8.5	14/11.3
	Ratio	1.75	1.40	1.17	1.24
	p-value	0.116	0.151	0.279	0.184
5 km	*Obs./Exp.*	15/9.9	28/19.7	36/29.4	51/38.9
	Ratio	1.52	1.42	1.22	1.31
	p-value	0.060	0.030	0.099	0.027
10 km	*Obs./Exp.*	26/23.9	53/47.9	68/71.5	95/94.4
	Ratio	1.09	1.11	0.95	1.01
	p-value	0.296	0.212	0.627	0.440

Table S9 Results of Knox tests of cases of leukaemia at place and time of diagnosis of children aged 0-15 years old

		Months			
		6	**12**	**18**	**24**
0.5 km	*Obs./Exp.*	13/13.3	23/26.4	40/39.2	53/51.8
	Ratio	0.97	0.87	1.02	1.02
	p-value	0.782	0.915	0.718	0.669
1 km	*Obs./Exp.*	38/36.9	64/72.9	106/108.5	140/143.4
	Ratio	1.03	0.88	0.98	0.98
	p-value	0.583	0.927	0.749	0.724
2 km	*Obs./Exp.*	91/101.3	180/200.2	283/297.9	372/393.5
	Ratio	0.90	0.90	0.95	0.95
	p-value	0.895	0.957	0.865	0.916
5 km	*Obs./Exp.*	339/373.0	690/737.0	1058/1096.7	1400/1448.7
	Ratio	0.91	0.94	0.96	0.97
	p-value	0.967	0.969	0.897	0.931
10 km	*Obs./Exp.*	904/946.6	1806/1870.5	2761/2783.4	3663/3676.8
	Ratio	0.95	0.97	0.99	1.00
	p-value	0.930	0.950	0.692	0.620

Table S10 Results of Knox tests of cases of leukaemia at place and time of diagnosis of children aged 0-4 years old

		Months			
		6	**12**	**18**	**24**
0.5 km	*Obs./Exp.*	5/4.0	10/8.1	14/12.0	19/15.9
	Ratio	1.24	1.24	1.16	1.19
	p-value	0.633	0.561	0.615	0.522
1 km	*Obs./Exp.*	15/9.8	23/19.7	33/29.4	43/38.9
	Ratio	1.53	1.17	1.12	1.11
	p-value	0.126	0.389	0.387	0.387
2 km	*Obs./Exp.*	31/26.7	61/53.5	81/79.7	105/105.6
	Ratio	1.16	1.14	1.02	0.99
	p-value	0.260	0.190	0.518	0.601
5 km	*Obs./Exp.*	103/101.9	208/204.2	300/304.4	391/403.2
	Ratio	1.01	1.02	0.99	0.97
	p-value	0.516	0.443	0.629	0.740
10 km	*Obs./Exp.*	257/248.7	494/498.4	743/743.0	975/984.0
	Ratio	1.03	0.99	1.00	0.99
	p-value	0.345	0.612	0.513	0.623

Table S11 Results of Knox tests of cases of leukaemia at place and time of diagnosis of children aged 5-15 years old

		Months			
		6	**12**	**18**	**24**
0.5 km	*Obs./Exp.*	4/3.3	4/6.4	11/9.6	13/12.6
	Ratio	1.21	0.62	1.15	1.03
	p-value	0.341	0.852	0.332	0.471
1 km	*Obs./Exp.*	10/8.3	13/16.2	22/24.2	27/31.8
	Ratio	1.20	0.80	0.91	0.85
	p-value	0.287	0.801	0.686	0.830
2 km	*Obs./Exp.*	21/22.9	31/44.6	52/66.7	67/87.7
	Ratio	0.92	0.69	0.78	0.76
	p-value	0.635	0.991	0.983	0.996
5 km	*Obs./Exp.*	61/84.3	128/164.1	221/245.1	293/322.4
	Ratio	0.72	0.78	0.90	0.91
	p-value	0.998	0.997	0.960	0.964
10 km	*Obs./Exp.*	183/223.3	371/434.5	619/648.8	823/853.4
	Ratio	0.82	0.85	0.95	0.96
	p-value	0.999	0.999	0.913	0.886

Table S12 Results of Knox tests of cases of acute lymphoid leukaemia at place and time of diagnosis of children aged 0-15 years old

		Months			
		6	**12**	**18**	**24**
0.5 km	*Obs./Exp.*	9/7.8	14/15.5	25/23.0	32/30.4
	Ratio	1.15	0.91	1.09	1.05
	p-value	0.608	0.861	0.595	0.613
1 km	*Obs./Exp.*	26/22.6	43/44.7	72/66.5	90/87.9
	Ratio	1.15	0.96	1.08	1.02
	p-value	0.382	0.746	0.361	0.526
2 km	*Obs./Exp.*	60/63.6	117/125.8	191/187.1	244/247.4
	Ratio	0.94	0.93	1.02	0.99
	p-value	0.734	0.837	0.440	0.651
5 km	*Obs./Exp.*	220/234.2	430/463.0	671/688.7	883/910.5
	Ratio	0.94	0.93	0.97	0.97
	p-value	0.846	0.959	0.789	0.853
10 km	*Obs./Exp.*	577/598.6	1142/1183.5	1755/1760.6	2346/2327.5
	Ratio	0.96	0.96	1.00	1.01
	p-value	0.845	0.913	0.577	0.389

Table S13 Results of Knox tests of cases of acute lymphoid leukaemia at place and time of diagnosis of children aged 0-4 years old

		Months			
		6	**12**	**18**	**24**
0.5 km	*Obs./Exp.*	5/2.9	8/5.7	12/8.5	14/11.3
	Ratio	1.74	1.39	1.41	1.24
	p-value	0.361	0.465	0.341	0.486
1 km	*Obs./Exp.*	11/6.9	17/13.7	26/20.4	32/27.0
	Ratio	1.60	1.24	1.27	1.19
	p-value	0.161	0.345	0.204	0.289
2 km	*Obs./Exp.*	18/19.1	40/38.1	57/56.6	72/74.9
	Ratio	0.94	1.05	1.01	0.96
	p-value	0.702	0.460	0.542	0.714
5 km	*Obs./Exp.*	68/72.6	140/144.8	206/214.9	266/284.5
	Ratio	0.94	0.97	0.96	0.94
	p-value	0.758	0.694	0.741	0.872
10 km	*Obs./Exp.*	176/176.7	345/352.3	520/523.0	687/692.2
	Ratio	1.00	0.98	0.99	0.99
	p-value	0.573	0.706	0.587	0.600

Table S14 Results of Knox tests of cases of acute lymphoid leukaemia at place and time of diagnosis of children aged 5-15 years old

		Months			
		6	**12**	**18**	**24**
0.5 km	*Obs./Exp.*	1/1.7	1/3.3	6/4.9	7/6.5
	Ratio	0.59	0.30	1.22	1.07
	p-value	0.679	0.920	0.319	0.447
1 km	*Obs./Exp.*	5/4.3	6/8.4	12/12.6	14/16.6
	Ratio	1.17	0.72	0.96	0.84
	p-value	0.340	0.805	0.556	0.769
2 km	*Obs./Exp.*	14/12.9	20/25.2	35/37.7	44/49.9
	Ratio	1.09	0.79	0.93	0.88
	p-value	0.338	0.859	0.677	0.833
5 km	*Obs./Exp.*	37/45.5	70/88.9	124/133.2	164/176.2
	Ratio	0.81	0.79	0.93	0.93
	p-value	0.910	0.989	0.819	0.853
10 km	*Obs./Exp.*	97/122.7	204/239.9	344/359.3	461/475.4
	Ratio	0.79	0.85	0.96	0.97
	p-value	0.994	0.996	0.829	0.798

Table S15 Results of Knox tests of cases of tumors of the central nervous system at place and time of diagnosis of children aged 0-15 years old

		Months			
		6	**12**	**18**	**24**
0.5 km	*Obs./Exp.*	8/6.9	18/13.7	22/20.5	31/27.2
	Ratio	1.16	1.31	1.07	1.14
	p-value	0.378	0.144	0.390	0.257
1 km	*Obs./Exp.*	20/20.0	41/39.8	61/59.3	82/78.6
	Ratio	1.00	1.03	1.03	1.04
	p-value	0.496	0.456	0.433	0.371
2 km	*Obs./Exp.*	49/51.4	102/102.3	143/152.5	186/202.2
	Ratio	0.95	1.00	0.94	0.92
	p-value	0.620	0.493	0.806	0.891
5 km	*Obs./Exp.*	197/196.2	403/390.2	577/581.6	764/770.8
	Ratio	1.00	1.03	0.99	0.99
	p-value	0.481	0.254	0.564	0.583
10 km	*Obs./Exp.*	492/471.8	972/938.5	1414/1398.8	1853/1854.1
	Ratio	1.04	1.04	1.01	1.00
	p-value	0.184	0.151	0.360	0.521

Table S16 Results of Knox tests of cases of lymphomas at place and time of diagnosis of children aged 0-15 years old

		Months			
		6	**12**	**18**	**24**
0.5 km	*Obs./Exp.*	5/2.8	6/5.6	7/8.4	8/11.0
	Ratio	1.77	1.07	0.84	0.72
	p-value	0.111	0.429	0.671	0.844
1 km	*Obs./Exp.*	9/7.1	14/14.1	22/21.0	28/27.8
	Ratio	1.27	0.99	1.05	1.01
	p-value	0.233	0.504	0.394	0.455
2 km	*Obs./Exp.*	25/19.7	43/39.2	63/58.6	76/77.3
	Ratio	1.27	1.10	1.08	0.98
	p-value	0.120	0.257	0.268	0.564
5 km	*Obs./Exp.*	78/76.5	147/152.0	215/227.2	292/299.8
	Ratio	1.02	0.97	0.95	0.97
	p-value	0.442	0.670	0.807	0.681
10 km	*Obs./Exp.*	186/181.2	342/359.8	514/537.7	684/709.6
	Ratio	1.03	0.95	0.96	0.96
	p-value	0.384	0.850	0.860	0.844

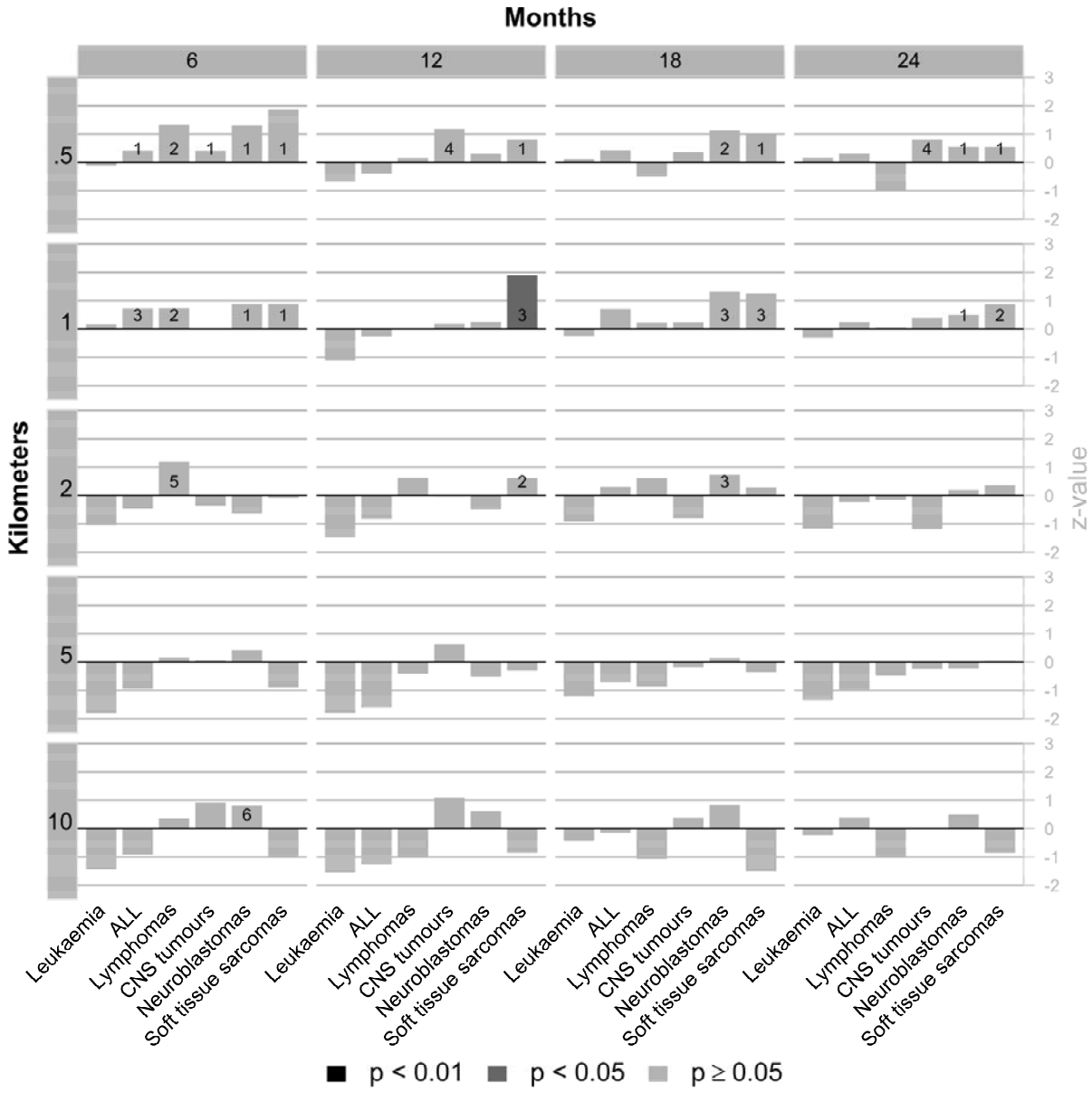
Table S17 Results of Knox tests of cases of neuroblastomas at place and time of diagnosis of children aged 0-15 years old

		Months			
		6	**12**	**18**	**24**
0.5 km	*Obs./Exp.*	2/0.8	2/1.6	4/2.4	4/3.1
	Ratio	2.39	1.23	1.69	1.29
	p-value	0.172	0.424	0.204	0.383
1 km	*Obs./Exp.*	3/1.8	4/3.6	8/5.2	8/6.8
	Ratio	1.64	1.12	1.54	1.17
	p-value	0.222	0.410	0.118	0.333
2 km	*Obs./Exp.*	4/5.4	9/10.5	18/15.3	21/20.2
	Ratio	0.74	0.85	1.17	1.04
	p-value	0.749	0.707	0.254	0.439
5 km	*Obs./Exp.*	22/20.1	36/39.1	58/56.9	73/74.8
	Ratio	1.10	0.92	1.02	0.98
	p-value	0.424	0.757	0.516	0.673
10 km	*Obs./Exp.*	56/50.4	104/98.1	152/142.7	194/187.8
	Ratio	1.11	1.06	1.07	1.03
	p-value	0.279	0.309	0.274	0.382

Table S18 Results of Knox tests of cases of soft tissue sarcomas at place and time of diagnosis of children aged 0-15 years old

		Months			
		6	**12**	**18**	**24**
0.5 km	*Obs./Exp.*	2/0.6	2/1.2	3/1.7	3/2.2
	Ratio	3.36	1.71	1.74	1.33
	p-value	0.077	0.237	0.189	0.304
1 km	*Obs./Exp.*	3/1.8	7/3.6	8/5.3	9/6.9
	Ratio	1.64	1.95	1.51	1.31
	p-value	0.201	0.046	0.143	0.211
2 km	*Obs./Exp.*	5/5.2	12/10.1	16/15.0	21/19.5
	Ratio	0.97	1.19	1.07	1.08
	p-value	0.526	0.289	0.397	0.351
5 km	*Obs./Exp.*	15/18.7	35/36.7	52/54.4	71/70.7
	Ratio	0.80	0.95	0.96	1.00
	p-value	0.843	0.654	0.658	0.525
10 km	*Obs./Exp.*	42/48.8	88/95.9	125/142.0	174/184.6
	Ratio	0.86	0.92	0.88	0.94
	p-value	0.860	0.811	0.952	0.828

Fig. S1 Standardized numbers of close pairs of cases in excess of expected numbers (z-values) for different diagnostic groups for all combinations of spatial and temporal lags around the place and time of diagnosis. Figures at the bottom of the bars indicate absolute numbers of excess close pairs



Erratum

Space-time clustering of childhood cancers in Switzerland: A nationwide study

Kreis, C., Grotzer, M., Hengartner, H., Daniel Spycher, B. and for the Swiss Paediatric Oncology Group and the Swiss National Cohort Study Group. Space-time clustering of childhood cancers in Switzerland: A nationwide study. Int. J. Cancer. 2016 May 1;138(9):2127–2135 doi:10.1002/ijc.29955. Epub 2016 January 8.

The published Table 2 reports the p-values of space-time clustering tests for the different diagnostic groups at place and time of diagnosis based on a Monte Carlo simulation that inadvertently used the reference date of the 2000 Swiss national census as date for the census in 2010 to sample the random controls from the general population. As a consequence, population figures, which during the first stage of the two-stage sampling procedure were used as weights to sample municipalities from which to sample the geocodes of actual control locations during the second stage, reflected the number of residents aged 10-25 years instead of 0-15 years in 2010. These population weights for part of the study period thus reflected an older share of the population than the cases. We therefore resampled controls using corrected weights and recalculated all tests. This does not alter the overall conclusion of the table: that at time of diagnosis there are no diagnostic groups of childhood cancer that show significant evidence of space-time clustering after correcting for multiple testing. (Population figures for analyses at time of birth were computed based on birth registry data instead of census data and remain unaffected.) The authors apologize for this error.

Table 2 Results of Space-Time Clustering Analysis by Diagnostic Group around Date/Place of Birth and Diagnosis Adjusted for Multiple Testing Using Baker's Max Method

	N	Date/Place of Birth	N	Date/Place of Diagnosis
Leukaemia, 0-15y	1052	0.045	1485	0.984
Leukaemia, 0-4y	631	0.607	753	0.652
Leukaemia, 5-15y	421	0.702	732	0.876
ALL, 0-15y	852	0.129	1185	0.919
ALL, 0-4y	519	0.822	628	0.717
ALL, 5-15y	333	0.876	557	0.894
CNS, 0-15y	689	0.765	996	0.648
Lymphomas, 0-15y	353	0.951	635	0.577
Neuroblastomas, 0-15y	268	0.188	310	0.609
Sarcomas, 0-15y	229	0.244	334	0.328