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ORIGINAL PAPER

Spatial clustering of childhood cancers in Switzerland: a nationwide study

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Abstract

Purpose Childhood cancers are rare and little is known about their etiology. Potential risk factors include environmental exposures that might implicate spatial variation of cancer risk. Previous studies of spatial clustering have mainly focused on childhood leukemia. We investigated spatial clustering of different childhood cancers in Switzerland using exact geocodes of place of residence.

Methods We included 6,034 cancer cases diagnosed at age 0–15 years during 1985–2015 from the Swiss Childhood Cancer Registry. Age and sex-matched controls (10 per case) were randomly sampled from the national censuses (1990, 2000, 2010). Geocodes of place of residence were available at birth and diagnosis for both cases and controls. We used the difference in k-functions and Cuzick–Edwards test to assess global clustering and Kulldorff's circular scan to detect individual clusters. We also carefully adjusted for multiple testing.

Results After adjusting for multiple testing, we found no evidence of spatial clustering of childhood cancers neither at birth ($p=0.43$) nor diagnosis ($p=0.13$). Disregarding multiple testing, results of individual tests indicated spatial clustering of all childhood cancers combined ($p<0.01$), childhood lymphoma ($p=0.01$), due to Hodgkin lymphoma (HL) ($p=0.02$) at diagnosis, and embryonal tumors of the central nervous system (CNS) at birth and diagnosis, respectively ($p=0.05$ and $p=0.02$).

Conclusions This study provides weak evidence of spatial clustering of childhood cancers. Evidence was strongest for HL and embryonal CNS tumors, adding to the current literature that these cancers cluster in space.

Keywords Cancer registry · Cancer clusters · Hodgkin lymphoma · Primitive neuroectodermal tumors · Medulloblastoma

Introduction

Childhood cancers are rare and little is known about possible environmental risk factors. For leukemia and central nervous system (CNS) tumors, the two most common cancer types in childhood, ionizing radiation in high doses is the only established environmental risk factor [1–3]. Infection with Epstein–Barr is thought to play a role in the etiology of Burkitt's lymphoma (BL) and Hodgkin lymphoma (HL) [4]. A number of other environmental exposures are suspected of causing cancer in children including low-dose ionizing radiation (e.g., natural background radiation or diagnostic radiology) [3], benzene [5, 6], traffic-related air pollution [7], and pesticides [8, 9]. However, despite numerous epidemiological studies, no firm conclusions regarding a causative role of these factors can yet be drawn.

Spatial variation of exposure to environmental factors may result in local aggregations of cancer cases. Such spatial

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aggregation might appear as distinct local clusters or as a general tendency of cases to occur closer to each other than would be expected if cases were homogenously distributed across the population (global clustering). Detecting spatial clustering or individual clusters could thus provide hints about underlying risk factors. Furthermore, the timing of spatial clustering might provide clues about age windows of susceptibility and latent periods. If the causative exposure occurs in utero or in early life, clustering would more likely be detected around time of birth (using address at birth). If on the other hand, the relevant exposure is closer to the time of diagnosis and latent periods are short, clustering would more likely be detected around the time of diagnosis (using address at diagnosis). Moreover, while etiologies, and thus clustering patterns, are likely to differ between diagnostic groups, some carcinogens such as ionizing radiation may increase the risk of multiple cancer types. It is thus also of interest to investigate spatial clustering of the combined group of all childhood cancers in addition to individual diagnostic groups.

More than 50 studies have investigated spatial clustering of childhood cancers, the majority of which focused on childhood leukemia [10, 11], including a previous study by the authors [12]. Fewer studies have investigated spatial clustering of other childhood cancers and these have focused on place of diagnosis, except for two studies that investigated residential locations at birth [13, 14]. A study from the UK reported evidence of spatial clustering of all cancers combined [15]. Based on cluster detection methods, childhood cancer clusters (all diagnostic groups combined) have been reported in Florida, Palestine, and Canada [16–18]. Studies from San Francisco and the UK have reported evidence of spatial clustering of HL, both supporting an association with Epstein–Barr virus (EBV) through correlation with deprivation [19, 20], whereas a study in Spain reported clustering of HL and non-Hodgkin lymphoma (NHL) in certain regions [21]. A study in Kenya reported spatial clustering of BL [22], further supporting the already established infectious etiology [23]. The aforementioned study from Palestine reported a cluster of childhood lymphoma [17]. The majority of studies investigating CNS tumors have not found evidence of spatial clustering [15, 21, 24–26], however, only few studies have investigated specific subtypes of CNS tumors. Evidence of spatial clustering was previously reported for medulloblastoma [24, 26].

Several methodological shortcomings limit the interpretability of these studies. Often only count data aggregated to administrative areal units (e.g., census tracts) were available, reducing the statistical power to detect clustering [27–29]. Results of spatial analyses using regional count data may vary considerably depending on the areal unit selected (modifiable areal unit problem) [30]. To our knowledge only one study has used precise geocodes [21]. Furthermore, most studies performed different statistical tests for different diagnostic or age groups without adjusting for the multiple tests performed [15, 18].

Following our previous analysis of spatial clustering of childhood leukemia [12], we aimed to investigate the spatial distribution of other childhood cancers in Switzerland including lymphomas, HL, NHL, CNS tumors, astrocytoma, intracranial and intraspinal embryonal tumors, other CNS tumors, neuroblastoma, nephroblastoma, malignant bone tumors, and soft tissue sarcomas. We also examined the combined group of all childhood cancers. We investigated spatial clustering at birth and diagnosis using geocoded places of residence, paying particular attention to appropriate correction for multiple testing.

Methods

Population

We included childhood cancer cases diagnosed at age 0–15 years in Switzerland during 1985–2015 from the Swiss Childhood Cancer Registry (SCCR). The SCCR is a national population-based cancer registry for children and adolescents in Switzerland with an estimated completeness of 91% since 1985 and 95% since 1995 [31]. The SCCR tracks residential address histories from diagnosis back to birth by contacting municipal population registers. Geocodes were obtained using the geo-referenced building addresses from the Swiss postal system (GeoPost) or manually localizing the buildings on the geoportal of the Federal Office of Topography (swisstopo; http://map.geo.admin.ch). For approximately 94% of the cases, we could geocode residential addresses with a margin of error < 100 m. For the remaining 6% we used a midpoint of the street, when the street name was available or a central residential location within the postal code area when only the postal code was known. Lastly, in order to avoid any influence of familial aggregation due to genetic factors, we included only one case from pairs of sibling cases.

Data for the population at risk were available from the Swiss National Cohort study [32] which includes the Swiss resident population at time of previous decennial questionnaire-based national censuses (1990, 2000) and the annual register-based censuses beginning in 2010. The data include geocoded place of residence at the time of censuses. Using a two-step weighted sampling procedure described in detail previously [33], we sampled 10 controls per case from this dataset matching on sex and timing of clustering. Thus for analyses of clustering at birth, we selected children aged < 1 year from the censuses closest in time to a case's birth, and for clustering at diagnosis we selected children matched for age at diagnosis from the censuses closest in

time to a case's diagnosis. The sampling procedure adjusts for regional population shifts between decennial censuses at the municipal level [33].

Outcomes

The SCCR codes diagnoses according to the International Classification of Childhood Cancer, third edition [34]. We investigated the following diagnostic groups: all cancers combined (groups I–XII), childhood lymphoma (II), HL (IIa), NHL (IIb, IIc, IId, IIe), CNS tumors (III), astrocytoma (IIIb), intracranial and intraspinal embryonal tumors (IIIc, here referred to as embryonal CNS tumors), other CNS tumors (IIIa, IIId, IIIe, IIIf), neuroblastoma (IV), nephroblastoma (VIa), malignant bone tumors (VIII), and soft tissues sarcomas (IX). These outcomes were chosen because the number of cases available at diagnosis exceeded the arbitrary threshold of 250 cases.

Statistical analysis

We used difference in k-functions [35] and Cuzick–Edwards test [36] to assess global clustering and Kulldorff's circular scan to detect local clusters [37]. Global clustering tests assess the preponderance of other cases over controls in the proximity of cases using different distance metrics: Euclidean distance (d) for difference in k-functions and the number of nearest neighbors (NN) for Cuzick–Edwards test. We selected a wide range of values for d (100, 250, 450, 600, 1,000, 1,500, 2,000, 3,000, 4,000, and 5,000 m) and corresponding values of NN based on the expected number of nearest neighbors within these distances given the number of cases and controls of each diagnostic group (see Supplementary Table S1). For Kulldorff's circular scan, the upper limit for the radii was set such that the resulting circles included half of the total number of case and control locations. The tests and their implementation are described in more detail elsewhere [12].

As in our previous investigation of childhood leukemia [12], we used Monte Carlo simulation to calculate p values for the tests (Supplementary Text S1) and to adjust for multiple testing at three levels (Supplementary Text S2). At a first level of adjustment, we calculated test statistics that accounted for the multiple input values used in each test, namely, the standardized maximum difference for k-functions [35], the minimum profile p value in Cuzick–Edwards test [36], and the maximum likelihood ratio for Kulldorff's circular scan [37]. We then generated 999 Monte Carlo samples by randomly permuting case and control labels given the locations, calculating the same statistics for each sample. We then calculated p values for the test statistics by ranking the empirical value of the test statistic among the corresponding values of the Monte Carlo samples and dividing the obtained rank by 1,000. Finally, we calculated the minimum of the p values from the first-level adjustment over the three statistical tests performed for each diagnostic subgroup (second-level adjustment) and minimum over all statistical tests and diagnostic groups (third-level adjustment) again obtaining p values by ranking these among corresponding values form the 999 Monte Carlo samples (see Supplementary Text S2 for more details). This correction for multiple testing is less conservative than a Bonferroni adjustment because it accounts for correlations between tests.

For residence at diagnosis, we ran a sensitivity analysis excluding the less precise geocodes (margin of error > 100 m).

Results

Study population

We identified 6,057 eligible cases of childhood cancer in the SCCR (Fig. 1). After excluding cases with missing geocodes and one record of each sibling pair, we included 6,034 cases for the analysis of spatial clustering at diagnosis. For the analysis at birth, we additionally excluded those born abroad or with uncertain place of birth and those born before 1985, leaving 4,078 cases available for analysis (Fig. 1). The age and sex distribution of included cancer cases follows the general pattern seen for different diagnostic groups in the SCCR and registries of neighboring countries (Table 1) [38, 39].

Clustering results

After adjusting for all tests performed (third-level adjustment), we found no evidence of global clustering or local clusters neither at birth (overall $p = 0.43$) nor diagnosis (overall $p = 0.13$) (Table 2). However, at the second level of adjustment, i.e., ignoring the fact that multiple diagnostic groups were investigated, our results were indicative of global clustering or clusters for the group of all cancers combined ($p = 0.01$) and childhood lymphoma ($p = 0.04$) at diagnosis and for embryonal CNS tumors at birth ($p = 0.05$) and diagnosis ($p = 0.02$). The evidence for lymphoma was stronger for HL ($p = 0.06$) than for NHL ($p = 0.43$).

In the analysis of all childhood cancers at diagnosis, the strongest evidence was obtained from k-functions at 4 km distances (adjusted $p < 0.01$, Table 2). Figure 2 shows that the evidence of clustering was strongest for distances larger than 500 m (top-left plot). The shaded area shows the typical range of values of the difference in k-functions in the absence of clustering (95% simulation envelopes under Monte Carlo sampling).

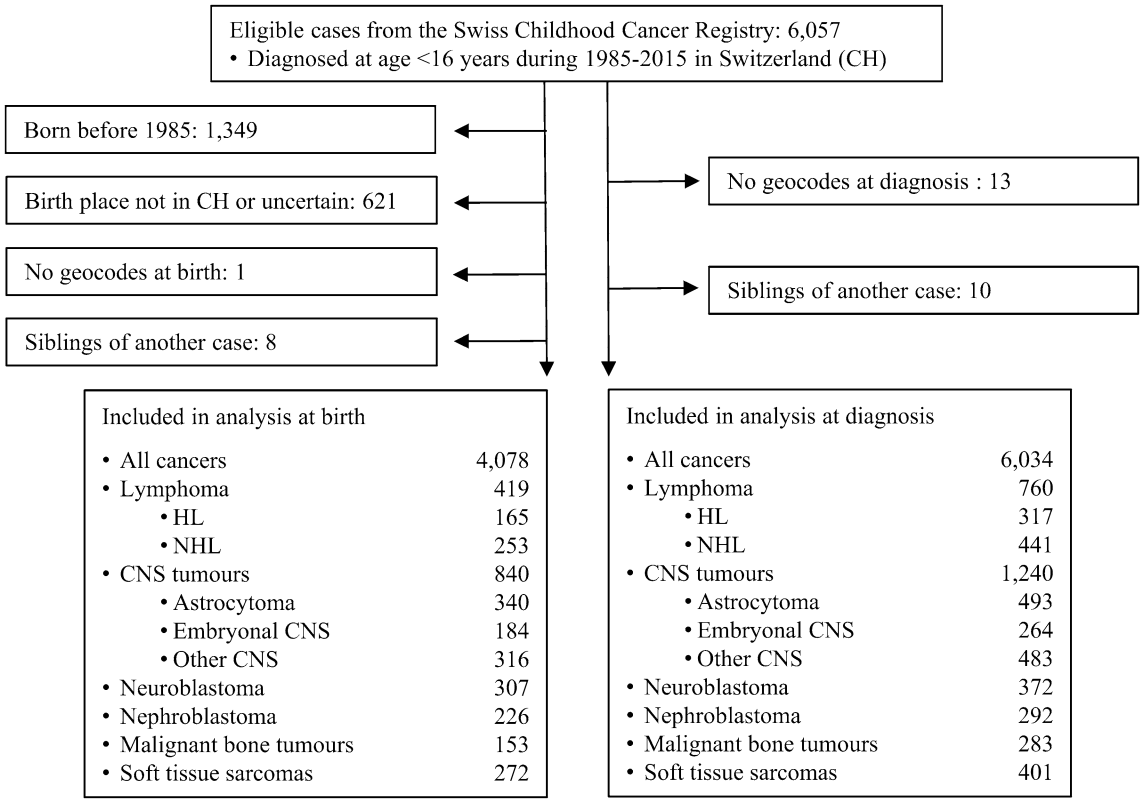

Fig. 1 Flow chart of the study population

Table 1 Characteristics of the cases included in the analysis of spatial clustering using residence at birth and at diagnosis

	Birth			Diagnosis		
	Number of cases		Age at diagnosis	Number of cases		Age at diagnosis
	Total	Female *n* (%)	Median	Total	Female *n* (%)	Median
All cancers[a]	4,078	1,826 (44.8)	4.6	6,034	2,694 (44.6)	6.3
Lymphoma	419	144 (34.4)	10.1	760	275 (36.2)	11.5
HL	165	71 (43.0)	13.3	317	149 (47.0)	13.7
NHL	253	74 (29.2)	6.9	441	127 (28.8)	8.8
CNS tumors	840	390 (46.4)	5.8	1,240	575 (46.4)	7.0
Astrocytoma	340	169 (49.7)	6.0	493	252 (51.1)	7.0
Embryonal CNS	184	70 (38.0)	5.6	264	96 (36.4)	6.3
Other CNS tumors	316	151 (47.8)	5.8	483	227 (47.0)	7.5
Neuroblastoma	307	154 (50.2)	1.0	372	183 (49.2)	1.3
Nephroblastoma	226	121 (53.5)	3.0	292	158 (54.1)	3.3
Malignant bone tumors	153	80 (52.3)	11.0	283	141 (49.8)	12.3
Soft tissue sarcomas	272	114 (41.9)	5.6	401	176 (43.9)	7.8

HL Hodgkin lymphoma, *NHL* non-Hodgkin lymphoma, *CNS* central nervous system

[a]Includes childhood leukemia cases ($n = 1,297$ and 1,865 for birth and diagnosis, respectively) which were the subject of a separate investigation [12]

In the analysis of childhood lymphoma, the strongest evidence for global clustering at diagnosis was observed for difference in k-functions at 3,000 m (adjusted $p = 0.01$, Table 2). The top-right plot in Fig. 2 indicates clustering for distances larger than 1,500 m. Strong evidence from the difference in k-functions was also observed for HL at a similar spatial scale (adjusted $p = 0.02$ at 3,000 m) but not

Table 2 Results of global clustering and cluster detection tests at birth or diagnosis

Diagnostic group	k-functions adjusted p[a] (d in m)	Cuzick–Edwards adjusted p[a] (k NN)	Kulldorff's scan adjusted p[a] (r in m)	Second-level adjusted p[b]
Birth				
All cancers[c]	0.11 (100)	0.18 (3)	0.94 (137)	0.28
Lymphoma	0.51 (3,000)	0.65 (7)	0.30 (2,209)	0.62
HL	0.31 (4,000)	0.51 (15)	0.73 (2,850)	0.58
NHL	0.77 (1,000)	0.69 (2)	0.36 (2,556)	0.66
CNS tumors	0.44 (100)	0.81 (1)	0.45 (4,287)	0.76
Astrocytoma	0.58 (1,000)	0.49 (11)	0.08 (3,598)	0.20
Embryonal CNS	0.43 (3,000)	0.50 (15)	0.02 (66,350)	0.05
Other CNS tumors	0.81 (4,000)	0.73 (15)	0.24 (8,640)	0.47
Neuroblastoma	0.62 (250)	0.76 (15)	0.47 (51,491)	0.75
Nephroblastoma	0.11 (1,000)	0.21 (15)	0.38 (12,291)	0.23
Malignant bone tumors	0.27 (600)	0.24 (3)	0.69 (2,620)	0.48
Soft tissue sarcomas	0.94 (3,000)	0.46 (11)	0.54 (4,275)	0.77
				Overall p[d] = 0.43
Diagnosis				
All cancers[c]	< 0.01 (4,000)	0.08 (1)	0.17 (8,550)	0.01
Lymphoma	0.01 (3,000)	0.56 (6)	0.44 (6,262)	0.04
HL	0.02 (3,000)	0.63 (2)	0.46 (4,582)	0.06
NHL	0.28 (600)	0.25 (4)	0.26 (577)	0.43
CNS tumors	0.20 (4,000)	0.05 (10)	0.24 (461)	0.13
Astrocytoma	0.21 (5,000)	0.16 (11)	0.30 (2,066)	0.37
Embryonal CNS	0.03 (450)	0.01 (2)	0.05 (17,400)	0.02
Other CNS tumors	0.63 (3,000)	0.12 (4)	0.10 (1,169)	0.24
Neuroblastoma	0.08 (5,000)	0.52 (1)	0.33 (61,818)	0.19
Nephroblastoma	0.89 (100)	0.61 (15)	0.05 (13,753)	0.13
Malignant bone tumors	0.39 (5,000)	0.59 (15)	0.89 (1,245)	0.68
Soft tissue sarcomas	0.82 (4,000)	0.33 (15)	0.10 (5,325)	0.24
				Overall p[d] = 0.13

HL Hodgkin lymphoma, *NHL* non-Hodgkin lymphoma, *CNS* central nervous system, *NN* nearest neighbors

[a]Data are p values adjusted for the different input values d, k, and r of the test (First-level adjustment, see Electronic Supplementary Material). The parameter for which the lowest p value was found is reported in parenthesis. For Kulldorff's circular scan, the latter represents the radius of the most likely cluster

[b]p value additionally adjusted for the different statistical tests performed in each diagnostic group

[c]Includes childhood leukemia cases (n = 1,297 and 1,865 for birth and diagnosis, respectively) which were the subject of a separate investigation [12].

[d]p value additionally adjusted for the different diagnostic groups considered including the all cancers combined group

for the NHL (adjusted $p = 0.28$ at 600 m) (Table 2; bottom plots in Fig. 2).

The strongest evidence for global clustering of embryonal CNS tumors was observed using Cuzick–Edwards test at diagnosis using 2 NN (adjusted $p = 0.01$) (Table 2), corresponding to distances of up to 1,400 m on average (Supplementary Table S1). The expected number of other cases among the 2 NN of a case was 47.79, whereas we observed 73 cases (Supplementary Table S2). Kulldorff's circular scan showed evidence of a cluster of embryonal CNS tumors at birth (adjusted $p = 0.02$, radius = 66,400 m) (Fig. 3). The cluster consisted of 66 cases, while the number of cases expected within this circle was 39.2, yielding a relative risk of 2.1. Weaker evidence was observed at diagnosis (adjusted $p = 0.05$, radius = 17,400 m) indicating a smaller cluster, nested in the above cluster (Fig. 3). The number of cases in this circle was 23 while 8.4 were expected, resulting a relative risk of 2.9.

When we considered only first-level corrections for multiple testing (i.e., correcting only for the different input

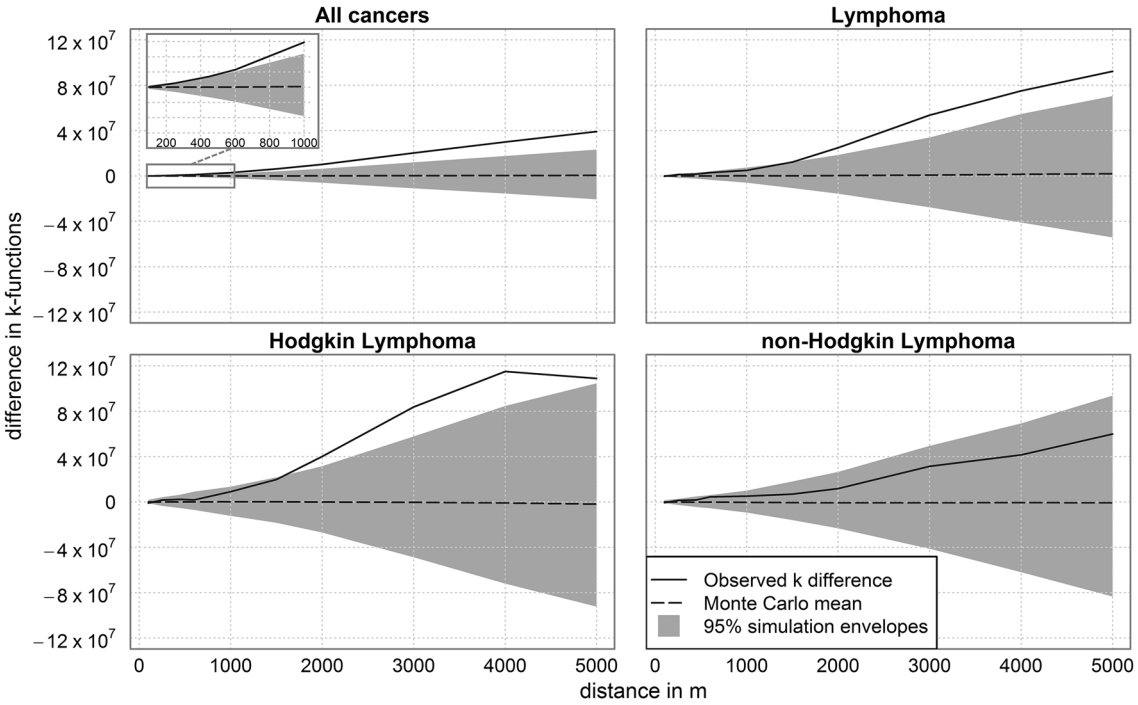

Fig. 2 The difference in k-functions for residence at diagnosis for all cancers combined, lymphoma, Hodgkin's lymphoma, and non-Hodgkin's lymphoma. The solid line shows the observed difference of the k-functions between cases and controls, whereas the dashed line indicates the mean difference observed in Monte Carlo samples in which the cases were randomly redistributed over locations (random labeling). The shaded area illustrates the 95% simulation envelopes (under random labeling) and values within it indicate no evidence of clustering. The inset plot in the top-left plot shows the difference in k-functions zoomed in on the smallest distances

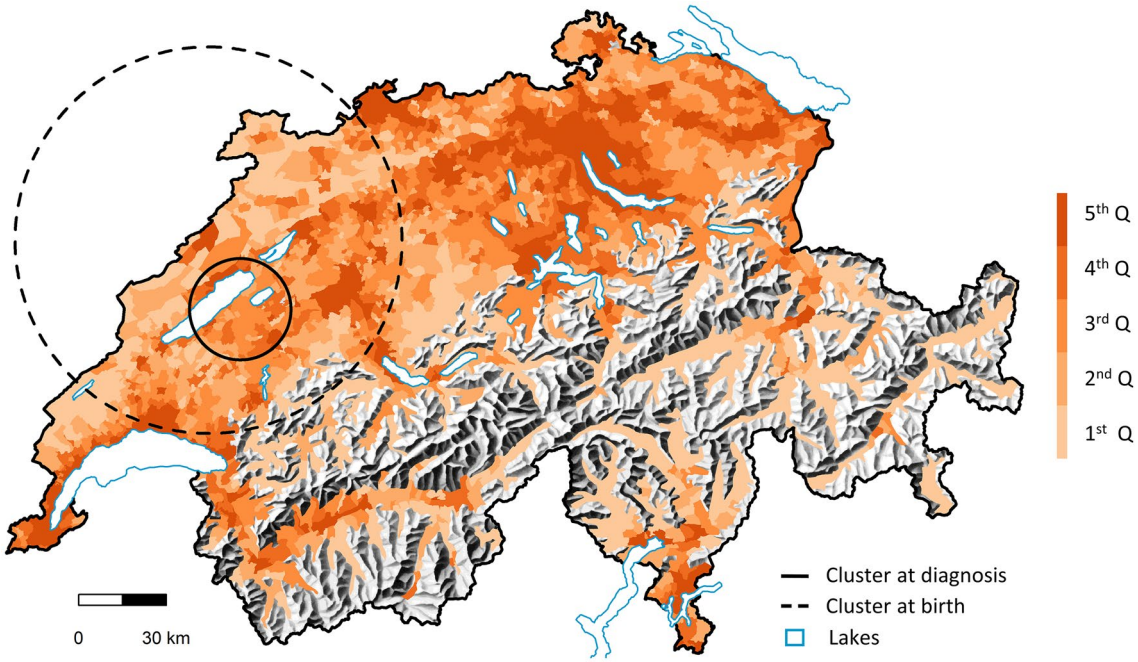

Fig. 3 The most likely cluster identified by Kulldorff's circular scan for embryonal CNS tumors for place of residence at birth (dashed circle) and at diagnosis (solid circle). The shading shows the population density per municipality in quintiles (*Q*), with darker colors indicating higher population density. (Color figure online)

values), our results were also indicative of global clustering of neuroblastoma (k-functions adjusted $p = 0.08$, at 5,000 m, Supplementary Fig. S1) and a cluster of nephroblastoma at diagnosis. This cluster consisted of 13 cases in a circle of almost 14 km. Based on Monte Carlo samples, the expected number of cases on that circle was 3.18.

Sensitivity analysis

When we excluded 361 geocodes with a margin of error > 100 m at diagnosis, p values tended to be lower. The overall evidence was strong (overall $p = 0.03$, Supplementary Table S3). In particular, stronger evidence of spatial clustering was found for all cancers (second level adjusted $p < 0.01$), childhood lymphoma (second level adjusted $p = 0.02$), HL (second level adjusted $p = 0.05$), and embryonal CNS tumors (second level adjusted $p = 0.03$) (Supplementary Table S3). For the group of all cancers, Kulldorff's scan statistic identified a cluster in the north-east of Switzerland (adjusted $p = 0.01$, radius = 23,199 m, Supplementary Table S3; Supplementary Fig. S4).

Post hoc analyses

In a post hoc analysis, we investigated the difference in k-functions for childhood lymphoma at diagnosis for distances up to 30 km, rather than up to 5 km only as in the main analysis. We observed evidence of clustering for distances up to 7 km (Supplementary Fig. S2).

We also investigated whether the clustering of lymphoma, embryonal CNS tumors, and neuroblastoma (based on the difference in k-functions results) accounted for the observed clustering of all cancers at diagnosis. We thus performed the difference in k-functions for the all cancers group excluding these diagnostic groups and observed no evidence of clustering (p k-functions = 0.16 at 5 km), (Supplementary Fig. S3).

Discussion

Summary of the results

This nationwide study investigated spatial clustering of childhood cancers in Switzerland during 1985–2015 using precise locations of residence. After correcting for the multiple testing resulting from investigating different diagnostic groups, we found no evidence of spatial clustering or of individual clusters, neither at birth nor at diagnosis. However, when considering diagnostic groups separately, we found evidence of clustering for the group of all cancers combined and for lymphoma at diagnosis, and for embryonal CNS tumors at birth and diagnosis. The evidence was stronger for HL than for NHL. The difference in k-functions suggested excesses of cases occurring near other cases for distances of 2–5 km for HL and 500 m to 3 km for embryonal CNS tumors. Kulldorff's circular scan identified a cluster of cases with embryonal CNS tumors in the north-west of Switzerland at birth (radius 66 km) and at diagnosis (radius 17 km). The evidence of clustering for the group of all cancers disappeared when lymphoma, embryonal CNS tumors, and neuroblastoma were excluded.

Discussion in the context of other studies

To our knowledge, a recent analysis of five regions in Spain is the only other study of spatial clustering of childhood cancers other than leukemia using precise geocodes of residence [21]. That study included 714 CNS tumors, 92 HL, and 246 NHL cases and 6 matched controls per case. The difference in k-function showed evidence of clustering for both HL and NHL in some regions, but not for CNS tumors. Kulldorff's circular scan found little evidence of spatial clusters, with the lowest p value (0.074) observed for a small aggregation of NHL cases in Madrid.

Few studies have applied global clustering tests or cluster detection methods to the group of all cancers combined. A large study from the UK including over 30,000 childhood cancer cases aggregated to census wards found evidence of clustering at diagnosis, which remained significant after excluding cases of lymphoma and leukemia [15, 40]. Evidence for local clusters of all cancers combined has been reported in studies from Florida [16], Palestine [17], and Canada [18]. The only other study that examined clustering of all cancers combined at birth was a study from the UK, which also found no evidence of clustering in agreement with our study [13].

The majority of studies investigating lymphoma as a group reported weak evidence of spatial clustering at diagnosis [15, 16, 21, 25]. One study reported evidence of a cluster of childhood lymphoma in Palestine [17], yet 53% of the included cases were BL. This result is not surprising since the geographical patterns of BL and its infectious etiology are known [22, 41]. In agreement with our study, other studies have also reported spatial clustering of HL at diagnosis [19–21, 42]—whereas the evidence from the mentioned, large UK study was weak [15]. A study in New Zealand found no evidence of global clustering of HL at birth [14]. Studies examining NHL have consistently reported no evidence of clustering [14, 15, 19].

Previous studies of spatial clustering of CNS tumors in children have, at most, found only weak evidence of global clustering or clusters [21, 24–26, 43]. In two studies that also examined major histologic subgroups, evidence of clustering was found for medulloblastoma [24] and the combined group of primitive neuroectodermal tumor (PNET) and medulloblastomas [26]. In our study, PNET and medulloblastomas

are the main tumor types subsumed as embryonal CNS tumors, for which we also found evidence of clustering. No evidence of spatial clustering has been reported for other CNS tumor types [24, 26, 43].

Few studies have assessed spatial clustering of other cancer diagnostic groups. Evidence for clustering was found in the UK for soft tissue sarcomas and Wilms tumors [15]. Studies investigating bone tumors separately or jointly with soft tissue sarcomas have reported weak evidence of clustering [15, 25].

Strengths and weaknesses

The main strength of our study is the use of precise locations of residence for both cases and representative controls. This avoids the modifiable areal unit problem and maximizes statistical power for detecting small-scale clustering [28, 30]. Cancer cases were obtained from a national registry with high coverage, and we were able to examine residence both at birth and at diagnosis. The use of different statistical tests made our analysis sensitive to different clustering patterns. Cuzick–Edwards test and the difference in k-functions are both sensitive to an overall tendency of cases to occur closer to each other than expected but use different proximity metrics (NN and Euclidean distance, respectively). Kulldorff's circular scan on the other hand is more sensitive to the presence of distinct clusters. We paid considerable attention to the multiple testing problem. In a previous analysis of childhood leukemia, we also included Tango's index as an additional test of global clustering but found that it was highly correlated with the difference in k-functions (see the Electronic Supplementary Material of our previous analysis [12]). We therefore decided not to use Tango's index for this analysis in order to mitigate the multiple testing problem. Lastly, we implemented a multiple testing approach that accounts for the correlation between tests and is less conservative than a Bonferroni approach.

While full address histories were known for cases, location of residence of controls was only available at census time points. We could thus not select control locations that were perfectly representative of the population at risk at cases' exact date of birth or diagnosis. However, we used a control sampling procedure that accounted for local population shifts in the years between the censuses. In order to minimize the multiple testing issue, we only used one cluster detection test, namely Kulldorff's circular scan, which is the most widely used scan statistic. A drawback of this scan statistic is that it only considers circular shapes and may thus have been insensitive to possible clusters of irregular shapes or clusters occurring at the country border and extending into the neighboring country, for which we had no data. Moreover, despite high completeness of the registry, our analyses missed a small proportion of cases, which may have reduced the statistical power of clustering tests. Lastly, geographical disparities in registration coverage may have affected our results. While the vast majority of childhood cancer cases are registered through specialized pediatric oncology centers, a small minority is identified through general cantonal cancer registries. However, not all cantons have a general cancer registry possibly leading to underreporting in these cantons. Kulldorff's scan compares the risk inside and outside defined circles. If there was systematic underreporting of cancer cases outside of certain circles, this could have led to spurious clusters. This is unlikely to have been the case for the clusters of embryonal CNS tumors identified in our analysis since the proportion of cases identified through cantonal registries was lower inside the clusters than outside: 0.02 against 0.06 for the cluster at birth and 0.05 against 0.07 for the cluster at diagnosis. In contrast, this might be a possible explanation for the cluster of all cancers reported in the sensitivity analysis (proportion of cases from cantonal registry 0.14 inside the circle against 0.05 outside).

Interpretation of findings

The fact that no evidence of spatial clustering for the combined group of all cancers remained when cases of lymphoma, embryonal CNS tumors, and neuroblastoma were excluded suggests that any spatial clustering of childhood cancers in Switzerland during the study period was mainly driven by these subgroups.

The clustering observed for lymphoma appears to be driven by HL. Spatial clustering of HL at diagnosis is consistent with the literature with 4 out of 6 studies reporting such evidence. The absence of distinct clusters and of clustering at birth may imply a late etiologic exposure to a ubiquitous agent promoting carcinogenesis [20]. Animal and epidemiological studies suggest that exposure to EBV could be such a promotor [4]. Possible socioeconomic factors associated with transmission of EBV or prevalence of EBV infection such as overcrowding [4] might cause spatial heterogeneity in incidence rates of HL. Other agents such as benzene might also play a role. However, there is little evidence of an association between HL and occupational benzene exposure in adults [44].

Our finding of global clustering of embryonal CNS tumors but not for other CNS tumors is also in agreement with the two other studies that have assessed medulloblastoma or PNET [24, 26] and suggests an etiologic factor specific to this tumor group. Of the 264 embryonal CNS tumor cases included in our study, 198 and 46 were medulloblastomas and PNET, respectively. The evidence of clustering was stronger at diagnosis, again suggesting a late etiologic exposure. Unfortunately, etiologic studies of childhood CNS tumors still rarely distinguish histologic subtypes. However, based on this literature, possible

etiological agents include insecticide use [45], *N*-nitroso compounds exposure [46], or traffic-related air pollution [47].

While adjustments for multiple testing indicate that our findings could be due to chance, the agreement with previous studies regarding HL and embryonal CNS tumors rather suggests that the observed clustering may have an environmental or infectious cause.

Conclusion

Our study adds further evidence that HL and embryonal CNS tumors in children tend to cluster in space due to post-natal environmental influences, which remain to be determined. Future etiological studies of childhood lymphoma and CNS tumors should stratify analyses by tumor subtypes and pool data to maximize power.

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Compliance with ethical standards

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 on 22 July 2014 (KEK-BE: 166/2014).

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