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External background ionizing radiation and childhood cancer: Update of a nationwide cohort analysis

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ABSTRACT

Background: Exposure to high doses of ionizing radiation is known to cause cancer. Exposure during childhood is associated with a greater excess relative risk for leukemia and tumors of the central nervous system (CNS) than exposure in later life. Cancer risks associated with low-dose exposure (<100 mSv) are uncertain. We previously investigated the association between the incidence of childhood cancer and levels of exposure to external background radiation from terrestrial gamma and cosmic rays in Switzerland using data from a nationwide census-based cohort study. Here, we provide an update of that study using an extended follow-up period and an improved exposure model.

Methods: We included all children 0–15 years of age registered in the Swiss national censuses 1990, 2000, and 2010–2015. We identified incident cancer cases during 1990–2016 using probabilistic record linkage with the Swiss Childhood Cancer Registry. Exposure to terrestrial and cosmic radiation at children's place of residence was estimated using geographic exposure models based on aerial spectrometric gamma-ray measurements. We estimated and included the contribution from ^{137}Cs deposition after the Chernobyl accident. We created a nested case-control sample and fitted conditional logistic regression models adjusting for sex, year of birth, neighborhood socioeconomic position, and modelled outdoor NO_2 concentration. We also estimated the population attributable fraction for childhood cancer due to external background radiation.

Results: We included 3,401,113 children and identified 3,137 incident cases of cancer, including 951 leukemia, 495 lymphoma, and 701 CNS tumor cases. Median follow-up in the cohort was 6.0 years (interquartile range: 4.3–10.1) and median cumulative exposure since birth was 8.2 mSv (range: 0–31.2). Hazard ratios per 1 mSv increase in cumulative dose of external background radiation were 1.04 (95% CI: 1.01–1.06) for all cancers combined, 1.06 (1.01–1.10) for leukemia, 1.03 (0.98–1.08) for lymphoma, and 1.06 (1.01–1.11) for CNS tumors. Adjustment for potential confounders had little effect on the results. Based on these results, the estimated population attributable fraction for leukemia and CNS tumors due to external background radiation was 32% (7–49%) and 34% (5–51%), respectively.

Conclusions: Our results suggest that background ionizing radiation contributes to the risk of leukemia and CNS tumors in children.

Abbreviations: ALL, Acute Lymphoblastic Leukemia; AML, Acute Myeloid Leukemia; CNS, Central Nervous System Tumor; ERR, Excess Relative Risk; GB, Great Britain; HR, Hazard Ratio; ICCC-3, International Classification of Childhood Cancer, Third edition; IQR, Interquartile Range; OR, Odds Ratio; PAF, Population Attributable Fraction; RBM, Red Bone Marrow; SCCR, Swiss Childhood Cancer Registry; SNC, Swiss National Cohort.

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1. Introduction

Ionizing radiation increases cancer risk in medium to high doses (UNSCEAR, 2006). For some types of cancer, relative increases in risk are higher following exposure during childhood (0–16 years of age) compared to exposure in adulthood (UNSCEAR, 2013). These include leukemia and tumors of the central nervous system (CNS), the most common childhood malignancies (Steliarova-Foucher et al., 2017). Leukemia is particularly sensitive to induction by radiation exposure, and disease onset may follow after a short latency of about two years (UNSCEAR, 2006). Low-dose exposure in the general population, for example, from background radiation or diagnostic radiology, may contribute to the risk of childhood cancer, particularly leukemia (Hauptmann et al., 2020; Laurent et al., 2013; Little et al., 2018; Wakeford et al., 2009).

Direct epidemiological evidence of the risk associated with low doses (<100 mSv) is difficult to obtain due to sample size requirements and the challenge of reliable dosimetry for large samples. Scientific committees generally assume that the risks associated with low doses can be extrapolated from linear/linear quadratic non-threshold models (LNT) developed from data of populations exposed to moderate and high doses, mainly from the Japanese atomic bomb survivors cohort (UNSCEAR, 2006). This assumption has been the subject of debate (Boice, 2017; Little et al., 2009b). However, the LNT model seems to be consistent with a majority of recent high-quality epidemiologic studies (Shore et al., 2018). Recent reviews suggest that low-dose exposure increases the risks for leukemia and CNS tumors (Berrington de Gonzalez et al., 2016; Hauptmann et al., 2020; Little et al., 2018). A pooled analysis of nine cohort studies including medically exposed populations and atomic bomb survivors found evidence of a positive dose-response relationship between the risk of acute leukemia and exposure at age <20 years to cumulative doses of <100 mSv (Little et al., 2018).

The excess cancer risks associated with low-dose ionizing radiation are expected to be small, and large sample sizes are needed to detect them. Achieving the required large sample sizes in studies based on interviews and measurements is difficult, and such studies have been underpowered (Kendall et al., 2021).

Over the last decade, several nationwide registry-based studies have investigated associations of exposure to natural background radiation and childhood cancer, mainly leukemia, with conflicting results (Berlivet et al., 2019; Demoury et al., 2016; Kendall et al., 2013; Nikkila et al., 2016; Spix et al., 2017; Spycher et al., 2015b). These studies relied on comprehensive cancer registries and other national routine datasets and required no active participation by study members, thereby minimizing the risk of selection bias. Nevertheless, a recent review of these studies highlighted the need for improved exposure models and increased sample sizes (Mazzei-Abba et al., 2020). A recent meta-analysis that included some of these studies and studies on medical exposure also reported a positive association between childhood leukemia and doses of <100 mSv (Hauptmann et al., 2020).

We aimed to investigate the association between external exposure to background gamma radiation and incidence of childhood cancers, including leukemias, lymphomas, and CNS tumors, in a nationwide cohort study in Switzerland. Given the diverse geology and topography of Switzerland, exposure to background radiation varies considerably by location. This study updates a previously published analysis of the same cohort, which reported increased risks of childhood leukemias and CNS tumors related to cumulative doses from external background radiation (Spycher et al., 2015b). The present study is based on a longer study period, a larger sample size, and an improved exposure model based on outdoor measurements. In the present study, we also estimate the population attributable fraction (PAF) for leukemias and CNS tumors due to external background radiation.

2. Methods

2.1. Population

Our study population consisted of children aged 0–15 years registered in the Swiss national censuses in 1990 and 2000 (decennial censuses) and 2010–2015 (annual population registry-based censuses). Data on this population were obtained from the Swiss National Cohort (SNC) study, a research platform linking the national censuses with national datasets on births, mortality, and migration (Spoerri et al., 2010). Records were linked probabilistically between the censuses of 1990, 2000, and 2011 and deterministically for the years 2010–2015. We obtained precise geocodes of children's places of residence which were available for census time points.

2.2. Outcomes

We identified incident cases of childhood cancer diagnosed during the study period 1990–2016 in the cohort through probabilistic record linkage of the SNC with the Swiss Childhood Cancer Registry (SCCR). The linkage was based on the variables sex, date of birth, maternal and paternal dates of birth, geocodes of residential address and municipality of residence at the census, and nationality. Incident cases among children who migrated into Switzerland after 2011 had not yet been linked at the time of analysis and were thus excluded from the cohort. The SCCR is estimated to include about 95% of all cancer diagnoses in Switzerland in the age group 0–15 years during the study period (Schindler et al., 2015).

We investigated the following outcomes, grouped according to the *International Classification of Childhood Cancers* (ICCC-3) (Steliarova-Foucher et al., 2005): any cancer type (ICCC-3 main groups I-XII), leukemias (ICCC-3 main group I), acute lymphoblastic leukemias (ALL) (ICCC-3 subgroup Ia), acute myeloid leukemias (AML) (Ib), lymphomas (II), CNS tumors (III), and other malignant tumors (IV–XII). Cases of Langerhans cell histiocytosis registered in the SCCR were included in the outcome group "other malignant tumors". For comparison with a previous study in France that examined CNS tumor subtypes and background radiation (Berlivet et al., 2019), we also examined ependymomas and plexus choroid tumors (IIIa), intracranial and intraspinal embryonal tumors (IIIc), gliomas (IIIb, IIId, IIIe4), and pilocytic astrocytomas separately from other gliomas.

2.3. Exposure assessment

We assessed exposure to external background radiation as the sum of the estimated exposures to natural terrestrial gamma radiation, cosmic radiation, and the gamma radiation originating from ^{137}Cs deposition after the Chernobyl accident. Exposure to terrestrial radiation was assessed as the outdoor ambient dose rate at children's place of residence at census based on a geographic exposure model developed by our team. The model has a resolution of 100 × 100m and is based on airborne gamma spectrometry measurements provided by the Swiss Federal Nuclear Safety Inspectorate (ENSI). The measurements were taken from a helicopter flying at roughly 90m altitude. The flight paths covered areas around nuclear facilities and areas of high population density. They included long-distance traversals across the country as well as targeted flights to sites of known local anomalies of natural sources. We fitted a Bayesian spatial model including over 40′000 measurements with the following predictor variables: maps of tectonics (19 categories) and lithology (5 categories) (geological maps provided by the Federal Office of Topography), land cover (6 categories, Federal Statistical Office) and cumulative daily rainfall following the Chernobyl accident to capture the effect of ^{137}Cs deposition (MeteoSwiss). The exposure model is described in more detail elsewhere (Folly et al., 2021).

The airborne measurements used to model terrestrial radiation were

mostly conducted after 2000, capturing ^{137}Cs-levels during the later part of our study period. In order to adjust for the higher levels of ^{137}Cs at the beginning of the study period, we first subtracted the contribution of ^{137}Cs from the developed model for terrestrial radiation and added a time-varying cesium component. The latter was modelled using as starting point a previously developed map of Switzerland showing concentrations of ^{137}Cs in 1989 (Rybach et al., 1996) and applying an exponential decay function over time (from 1986 to 2015). The decay rate was estimated using measurements of ^{137}Cs levels taken during 1989–2018 at 26 fixed locations across the country (see Appendix A for more details). Finally, we estimated exposure to cosmic rays as a deterministic function of altitude at the residential address: Dose rate [nSv/h] = 37.0 exp (0.38 altitude [km]) (Bundesamt fuer Gesundheitswesen, 1994).

2.4. Potential confounders and covariates

We adjusted our models for potential confounding by the degree of urbanization at the municipal level (urban, peri-urban, rural), socioeconomic status (Swiss neighborhood index of socioeconomic position assessed in 2000 based on median rent, education and occupation of household heads, and household crowding, in quintiles) (Adam et al., 2015; Panczak et al., 2012), and traffic-related air pollution (modelled annual mean ambient air concentration of NO_2, time-varying covariate). We also adjusted for the presence of a cantonal cancer registry in certain regions during the observation period (annually time-varying). The SCCR has nationwide coverage, but registration is expected to be slightly more complete in cantons with a general cantonal registry, as data from these registries were used to register any cases missed out by the SCCR.

2.5. Statistical analyses

Children entered the cohort on the date of the first census, in which a child was recorded with complete address information, and were considered at risk until diagnosis, death, emigration, 16th birthday, loss to follow-up, or administrative censoring at the end of follow-up (December 31st, 2016), whichever occurred first. For children who relocated between censuses, exposure was adjusted to the precise date of relocation, if known, or to the mid-point between the two nearest time points with a known location. We thus reconstructed address histories to the full extent possible using all available residential address information.

As exposure variables we considered i) cumulative dose in mSv since birth and ii) ambient dose rate in nSv/h at entry into the cohort. We calculated cumulative exposure by integrating the total dose rate from birth to diagnosis. We also considered cumulative exposure lagged by 24 months and 5 years to account for the lag time between exposure and potential development of cancer (UNSCEAR, 2006). We included exposure variables both as continuous (entered as a linear term) and categorical variables in separate models. To define categories, we used regularly spaced intervals (4 mSv for cumulative exposure and 25 nSv/h for dose rate) around the median and merged neighboring categories until no interval contained less than 1% of the total population.

To reduce the computational burden and facilitate the analysis of a time-varying exposure (cumulative dose), we created a nested case-control dataset. We randomly sampled 100 controls per case without replacement from the population at risk at the time of a case's diagnosis (risk set sampling), additionally matching on year of birth. We fitted conditional logistic regression models conditioning on the matched case-control sets. This procedure is asymptotically (with increasing sample size) equivalent to Cox proportional hazards regression using the full cohort with age as the underlying time scale (Goldstein and Langholz, 1992). Given this equivalence, we refer to the odds ratios estimated from these conditional logistic regression models as hazard ratios. All models were adjusted for sex (minimally adjusted models), while, in separate models, we adjusted for the other potential confounders (fully adjusted models).

To investigate the potential impact of exposure misclassification, we conducted a sensitivity analysis by restricting the cohort to children with a stable place of residence before entry into the cohort or with fully known address histories.

For leukemia and CNS tumors, we also estimated the population attributable fraction (PAF) and the annual attributable number of childhood cancer cases due to cumulative exposure to external background radiation. These calculations were based on the estimated dose coefficients from models including a linear exposure term and on age-specific cancer incidence rates and exposure distributions during the period 2000–2015 (see Appendix B for details).

3. Results

The SNC included a total of 3,493,769 children 0–15 years of age who contributed 24,6 million person-years at risk during the period of 1990–2016. After excluding children who migrated into Switzerland after 2011 (see methods), the final analysis included 3,401,113 children and 24.4 million person-years at risk (Table 1). Median age of children at entry into the cohort was 5.4 years (interquartile range (IQR): 1.9–9.0) and median total follow-up time was 6.0 years (IQR: 4.3–10.1). In the SCCR, we identified 5,627 childhood cancer cases diagnosed during the study period. Of these, 3,137 could be linked to the cohort and were available for analysis (Fig. 1) including 951 cases of leukemia, 495 cases of lymphoma, 701 cases of CNS tumors, and 990 cases of other malignant tumors.

Table 1
Characteristics of the study population at the time of entry into the cohort[a].

	N (%)	Person-years	Cancer cases
Total	3,401,113 (100)	24,432,588	3,137
Sex			
Male	1,745,303 (51.3)	12,525,252	1,743
Female	1,655,810 (48.7)	11,907,336	1,394
Year of birth			
1974–1979	379,591 (11.2)	948,126	71
1980–1989	837,680 (24.6)	7,791,602	832
1990–1999	880,751 (25.9)	8,797,102	1,176
2000–2009	806,430 (23.7)	5,230,766	771
2010–2015	496,661 (14.6)	1,664,992	287
Year of entry into cohort			
1990	1,238,297 (36.4)	9,724,639	1,067
2000	865,470 (25.4)	8,662,554	1,140
2010	848,353 (24.9)	4,732,456	711
2011–2015	448,993 (13.2)	1,312,939	219
Degree of urbanization			
Urban	861,574 (25.3)	5,772,791	783
Peri-urban	1,558,566 (45.8)	11,252,160	1,447
Rural	980,973 (28.8)	7,407,638	907
Swiss-SEP index			
1st quintile (low SEP)	901,274 (26.5)	6,305,009	828
2nd quintile	701,515 (20.6)	5,052,884	613
3rd quintile	648,841 (19.1)	4,721,496	626
4th quintile	613,232 (18.0)	4,495,890	582
5th quintile (high SEP)	536,251 (15.8)	3,857,310	488
NO_2			
1st quartile	804,267 (23.6)	6,569,155	738
2nd quartile	802,972 (23.6)	6,237,041	731
3rd quartile	851,467 (25.0)	6,114,959	772
4th quartile	942,142 (27.7)	5,509,605	895
Missing	265		
External background radiation (nSv/h) at entry in the cohort			
0 - <100	2,154,243 (63.3)	15,131,249	1,948
100 - <125	1,031,379 (30.3)	7,731,894	961
125 - <150	99,394 (2.9)	676,446	93
150 - 264	1,16,097 (3.4)	892,998	135

Abbreviations
SEP: Swiss neighborhood index of socioeconomic position.
[a] Time of entry into cohort corresponds to the first census in which the child was recorded with full address information.

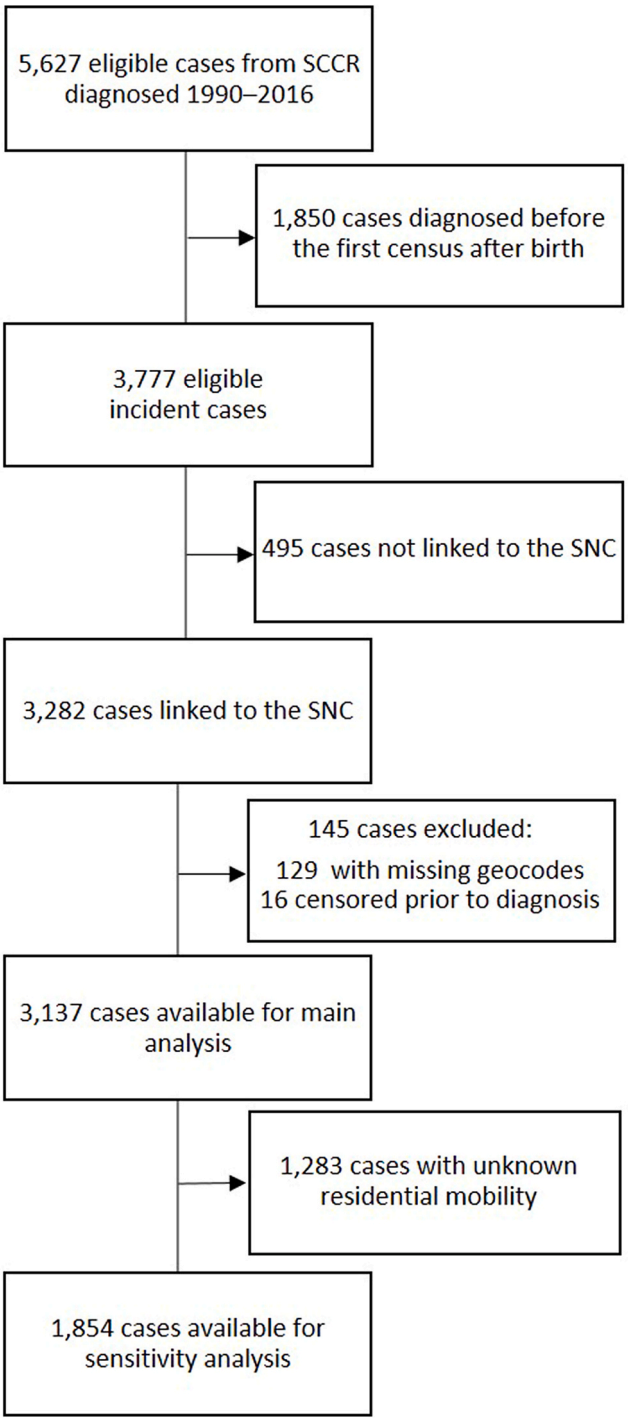

Fig. 1. Flow chart of childhood cancer cases included in analyses.
Abbreviations
SCCR: Swiss Childhood Cancer Registry
SNC: Swiss National Cohort

Children's median exposure to external background radiation at entry into the cohort was 96.4 nSv/h (range: 62.5–263.2) (Fig. 2 and Table C1 in appendix). The terrestrial gamma component contributed most to children's total dose and also showed the highest variability between individuals (median: 47.5 nSv/h, range: 16.3–168.3). In the nested case-control sample, median cumulative exposure since birth among controls, assessed at the age of diagnosis of the matched case, was 8.2 mSv (range: 0–31.2) (Fig. 2 and Table C1 in the appendix).

In conditional logistic regression analyses, we found evidence of a positive association between cumulative dose since birth, included as a linear term, and the risk of any cancer (fully adjusted HR per mSv: 1.04; 95% CI: 1.01–1.06), leukemia (1.06; 1.01–1.10), CNS tumors (1.06; 1.01–1.11), AML (1.09; 0.99–1.19), and ALL (1.04; 0.98–1.10) (Table 2 upper panel). We observed similar positive associations for all subtypes of CNS tumors. Our results were similar when considering a latent period of 24 months (Table 2, lower panel). When considering a 5-year latency period, results were similar, however, sample size was considerably reduced and confidence intervals were larger (Table C2). For CNS tumors confidence intervals where compatible with no association, while associations for leukaemia were somewhat stronger. When including cumulative exposure as a categorical exposure variable, risks were consistently higher for the highest exposure category (>12 mSv) compared to the baseline category (<4 mSv) for all main groups of childhood cancer (Fig. 3 and Table C3 in the appendix), but confidence intervals were large.

Analyses of cancer risks by ambient dose rate at children's homes at entry into the cohort showed a similar pattern. The adjusted HR for a difference of 100 nSv/h in ambient dose rate for all cancers combined was 1.35 (1.11–1.65) and 1.33 (0.93–1.90) for leukemia. The strongest associations were again seen for AML (1.92; 0.83–4.40) and CNS tumors (1.49; 0.98–2.25) (Table 3). When using categories of exposure, the risk was higher for children exposed to doses of >150 nSv/h compared to those exposed to <100 nSv/h for all the main cancer subtypes (Table C4 in the appendix), but confidence intervals were again wide.

The sensitivity analysis, including only children with stable residence or with fully known address history, included 1,764,131 children (51.8% of the entire cohort) and 1,854 cancer cases. In this subcohort, associations with cumulative dose were higher for leukemia (1.08; 1.02–1.15) and ALL (1.08; 1.00–1.15) but lower for CNS tumors (1.02; 0.96–1.09) compared to the main analyses (Table C5 and C6 in the appendix). Results were similar for minimally adjusted and fully adjusted models (Table C3 and C4).

The PAF was estimated at 32.2% (7.0–49.3) for leukemia and 33.6% (5.5–51.0) for CNS tumors (Table 4).

4. Discussion

This study found renewed evidence that exposure to higher levels of external background ionizing radiation is associated with an increased risk of childhood cancer. In the analysis of cumulative dose received since birth, the risks were higher for leukemia and CNS tumors compared to other outcomes. We also found evidence of an increased risk of childhood cancer with ambient dose rate. Our estimation of the PAF suggests that a considerable fraction of childhood leukemia and CNS tumor cases might be caused by exposure to external background radiation. Adjustments for potential confounding had little effect on the results of the analyses.

Our results are consistent with the previous study in Switzerland, which reported an HR per mSv of 1.04 (1.00–1.08) for leukemia and 1.04 (1.00–1.08) for CNS tumors (Spycher et al., 2015b) (Table C7). The data sources of these two studies are identical and overlap for the period 1990–2008. In the present study, however, we extended the follow-up until 2016, and thus almost doubled the number of included leukemia and CNS tumor cases, adding to the statistical power of the study. Also, the present analysis is based on an improved exposure model. Compared to the previous study (Rybach et al., 1996, 2002), the present model was based on a broader and denser coverage of populated areas, including the major cities but also rural and mountainous areas (Folly et al., 2021). The broader coverage of measurements and inclusion of a time-varying cesium component have likely reduced exposure misclassification, particularly in the canton of Ticino, where the contribution from ^{137}Cs to exposure in the general population was substantial.

The extrapolations from standard risk models developed using data from atomic bomb survivors suggest that an excess relative risk (ERR) of around 5% per mSv for leukemia might be applicable to a population

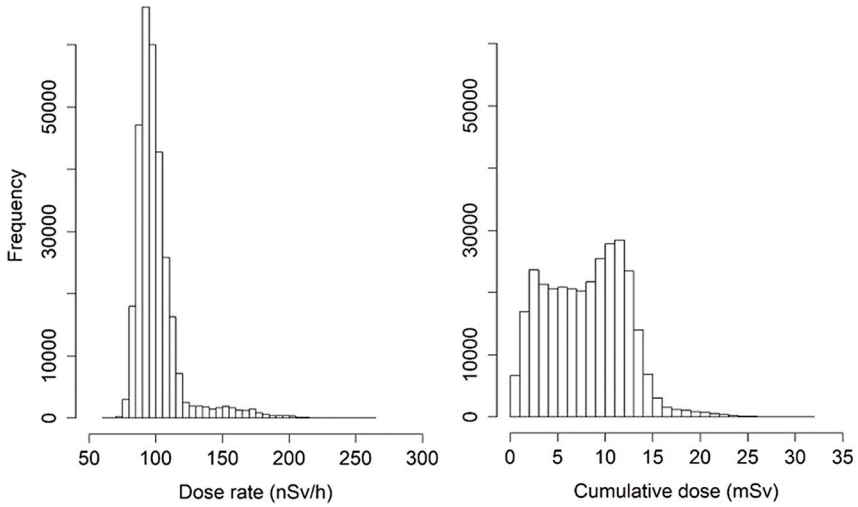

Fig. 2. Ambient dose rate (left) and cumulative doses since birth (right) from external background radiation.
Values for ambient dose rate are at the time of entry into the cohort.

Table 2
Hazard ratio (HR) for childhood cancer per mSv increase in cumulative equivalent dose from external background radiation.

		Minimally adjusted [a]	Fully adjusted [b]
	Cases	HR[c] (95% CI)	HR[c] (95% CI)
0 months latency period			
All cancers	3,137	1.03 (1.01, 1.06)	1.04 (1.01, 1.06)
Leukemia	951	1.04 (1.00, 1.09)	1.06 (1.01, 1.10)
ALL	754	1.03 (0.98, 1.08)	1.04 (0.98, 1.10)
AML	133	1.07 (0.98, 1.17)	1.09 (0.99, 1.19)
Lymphoma	495	1.02 (0.97, 1.07)	1.03 (0.98, 1.08)
CNS tumor	701	1.06 (1.01, 1.11)	1.06 (1.01, 1.11)
Ependymomas	52	1.11 (0.94, 1.30)	1.09 (0.92, 1.30)
Embryonal tumor	129	1.09 (0.99, 1.21)	1.09 (0.98, 1.21)
Gliomas	425	1.05 (0.99, 1.11)	1.05 (0.98, 1.11)
Pilocytic astrocytomas	178	1.03 (0.93, 1.13)	1.01 (0.91, 1.13)
Other gliomas	247	1.06 (0.98, 1.14)	1.06 (0.98, 1.15)
Other	990	1.02 (0.98, 1.06)	1.01 (0.97, 1.06)
24 months latency period			
All cancers	2,248	1.04 (1.01, 1.07)	1.04 (1.01, 1.07)
Leukemia	615	1.05 (0.99, 1.11)	1.06 (1.00, 1.13)
ALL	479	1.03 (0.96, 1.10)	1.04 (0.97, 1.12)
AML	94	1.10 (0.99, 1.22)	1.11 (0.99, 1.23)
Lymphoma	415	1.01 (0.96, 1.08)	1.03 (0.97, 1.09)
CNS tumor	521	1.08 (1.02, 1.14)	1.06 (1.00, 1.13)
Ependymomas	28	1.13 (0.91, 1.41)	1.09 (0.86, 1.39)
Embryonal tumor	95	1.13 (1.00, 1.29)	1.11 (0.97, 1.27)
Gliomas	314	1.05 (0.98, 1.14)	1.04 (0.96, 1.13)
Pilocytic astrocytomas	130	1.04 (0.93, 1.17)	1.00 (0.88, 1.15)
Other gliomas	184	1.06 (0.97, 1.17)	1.07 (0.96, 1.18)
Other	697	1.02 (0.98, 1.07)	1.00 (0.95, 1.06)

Abreviations:
ALL: Acute Lymphoid Leukemia
AML: Acute Myeloid Leukemia
CNS: Central Nervous System.

[a] Models adjusted only by sex.

[b] Models adjusted by sex, degree of urbanization, availability of cantonal cancer registry, quintiles of socioeconomic status, and NO_2. In the fully adjusted analysis, one case of CNS tumors (glioma) was not included as its value for NO_2 was not available.

[c] HRs are obtained as the odds ratios from conditional logistic regression models fitted to nested case-control datasets matched on age (risk set sampling) and year of birth.

exposed to low doses in early life (Wakeford, 2013). In the present study, we found a relative risk of 1.06 (95% CI: 1.01–1.10) per mSv corresponding to an ERR of 6% per mSv, which is in broad agreement with these extrapolations, although still fraught with large uncertainties. Based on the extrapolations from standard risk models, risk assessment studies estimated that the proportion of cases of childhood leukemia due to exposure to natural sources of radiation (including external radiation and inhaled radon) may be as high as 20% in France and Great Britain (GB) (Laurent et al., 2013; Little et al., 2009a). Based on direct estimation of risks associated with background radiation in Switzerland, we estimate this proportion to be 32% (7–49%) from external radiation alone. However, the uncertainty in all studies is large and caution is required in applying these risk models derived from populations exposed acutely to medium and high doses to protracted exposure to low-dose rates (Little et al., 2009b).

Studies of areas of high natural background radiation have been conducted in Kerala, India and Yangjiang, China and found little or no effect after low dose-rate exposures. However, these studies have several limitations that hinder the interpretation of results: substantial uncertainties in dosimetry, the weaknesses in cancer ascertainment in Yangjiang, low statistical power, and potential confounding by variations in lifestyles and risk factors in the different geographic regions associated with different levels of radiation (Shore et al., 2018). Importantly, these studies did not include children.

Over the last decade, other European countries have conducted similar studies to the present one with conflicting results. A detailed comparison of their methodologies and results can be found elsewhere (Mazzei-Abba et al., 2020). Our results for leukemia are consistent with a record-based case–control study conducted in GB by Kendall and colleagues (Kendall et al., 2013). Compared to our study, their point estimates per mSv cumulative dose, measured as equivalent dose to the red bone marrow (RBM), were larger for leukemia (OR: 1.12, 95% CI: 1.03–1.22) and smaller for CNS tumors (1.02, 95% CI: 0.96–1.09). In contrast, a large register-based study from France found no evidence of increased risks for childhood leukemia related to terrestrial gamma radiation, reporting confidence intervals for the RR per mSv of cumulative dose to the RBM centered narrowly around 1 (RR: 1.00, 95% CI: 0.99–1.01) (Demoury et al., 2016). A nationwide case-control study in Finland found no evidence of an association with childhood leukemia (RR: 1.01, 95% CI: 0.97–1.05 for 1 mSv unit increase in cumulative dose to RBM from terrestrial gamma); however, in subgroup analyses, leukemia diagnosed at ages 2–6 years was positively associated with cumulative dose (1.27, 95% CI: 1.01–1.60) (Nikkila et al., 2016). A recent ecological study from Germany including a large number of cases found no evidence of an association between childhood leukemia rates and mean gamma-ray exposure at the municipality level (Spix et al., 2017), but confidence intervals were compatible with the findings of other

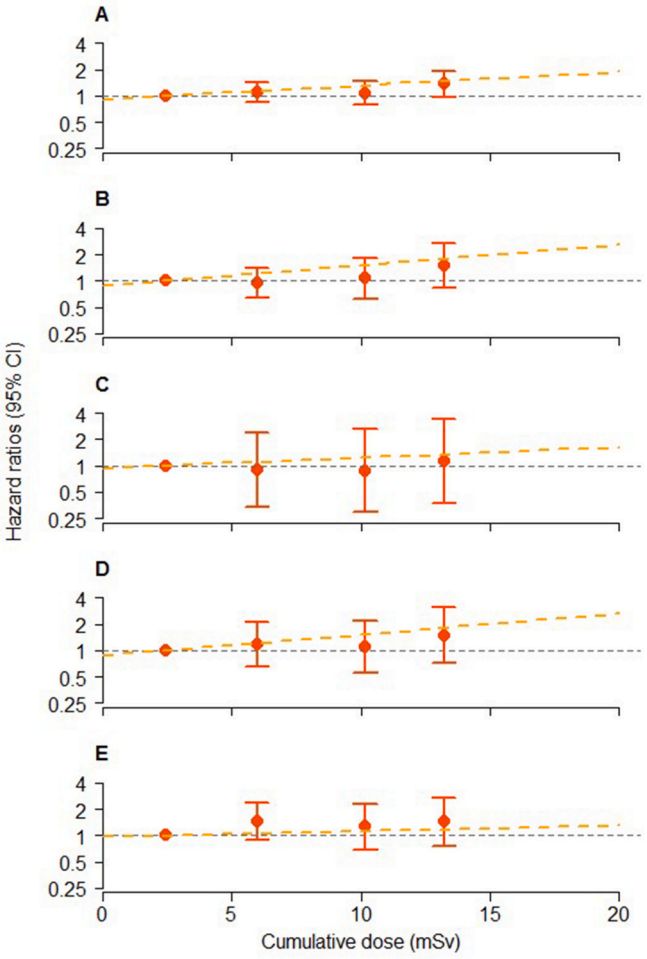

Fig. 3. Hazard ratios (HR) for cancer by categories of cumulative dose from external background radiation.
Hazard ratios for A) All cancers combined; B) Leukemia; C) Lymphoma; D) CNS tumors; and E) Other cancers. The dashed grey line indicates a hazard ratio of 1. The point estimates show the fitted model with a categorical exposure term and are placed at median cumulative dose within categories. The dose boundaries used for categories are 0, 4, 8, 12, and 30 mSv with risk in the 0–4 mSv group defining the baseline risk. The dashed orange line shows the fitted model with a linear exposure term. The line is vertically placed so as to pass through 1 at the median dose of the baseline category. This choice is, however, arbitrary as conditional logistic regression models do not include an intercept.

studies including this one.

The evidence base on childhood CNS tumors and background radiation is smaller than for leukemia. The most recent study, an ecological study from France, reported a positive association only for the subgroup of pilocytic astrocytoma with an incidence rate ratio of 1.15 (95% CI: 0.99–1.33) per 5 mSv difference in cumulative gamma dose (Berlivet et al., 2019). For comparison purposes, we explored the association with pilocytic astrocytoma in our cohort, finding little evidence of an association (1.05; 0.62–1.84 per 5 mSv). In Germany, an ecological study reported a relative risk of 1.35 (95% CI: 1.17–1.57) for childhood CNS tumors, comparing a gamma dose rate of 1.5 mSv/y to 0.5 mSv/y (Spix et al., 2017). Both these studies are in agreement with our results. However, the elevated risks found for CNS tumors were considerably reduced in our study when restricting the analysis to the cohort of children with known residential history for whom the risk of exposure misclassification was smaller (Table C6).

We found little evidence of an association for lymphoma, which is consitent with the lack of evidence from most studies that investigated

Table 3
Hazard rations (HR) for childhood cancer per 100nSv/h increase in ambient dose rate of external background radiation at entry into cohort.

	Cases	Minimally adjusted[a] HR[c] per 100nSv/h (95% CI)	Fully adjusted[b] HR[c] per 100nSv/h (95% CI)
0 months latency period			
All cancers	3,137	1.32 (1.10, 1.59)	1.35 (1.11, 1.65)
Leukemia	951	1.20 (0.85, 1.71)	1.33 (0.93, 1.90)
ALL	754	1.08 (0.71, 1.62)	1.17 (0.77, 1.79)
AML	133	1.71 (0.75, 3.92)	1.92 (0.83, 4.40)
Lymphoma	495	1.17 (0.73, 1.87)	1.27 (0.78, 2.05)
CNS tumor	701	1.52 (1.03, 2.24)	1.49 (0.98, 2.25)
Ependymomas	52	2.49 (0.69, 8.94)	2.27 (0.57, 9.09)
Embryonal tumor	129	2.02 (0.89, 4.58)	2.03 (0.87, 4.70)
Gliomas	425	1.34 (0.79, 2.25)	1.29 (0.73, 2.28)
Pilocytic astrocytomas	178	0.98 (0.40, 2.39)	0.84 (0.31, 2.25)
Other gliomas	247	1.60 (0.84, 3.04)	1.61 (0.81, 3.21)
Other	990	1.38 (1.00, 1.92)	1.33 (0.94, 1.87)
24 months latency period			
All cancers	2,248	1.36 (1.10, 1.70)	1.32 (1.05, 1.66)
Leukemia	615	1.30 (0.85, 2.01)	1.44 (0.93, 2.25)
ALL	479	1.09 (0.65, 1.83)	1.25 (0.73, 2.14)
AML	94	2.02 (0.80, 5.08)	2.12 (0.85, 5.33)
Lymphoma	415	1.11 (0.65, 1.88)	1.24 (0.72, 2.13)
CNS tumor	521	1.83 (1.19, 2.79)	1.62 (1.02, 2.57)
Ependymomas	28	4.70 (1.09, 20.24)	3.95 (0.8, 19.58)
Embryonal tumor	95	2.63 (1.09, 6.36)	2.35 (0.92, 6.02)
Gliomas	314	1.48 (0.83, 2.65)	1.28 (0.67, 2.46)
Pilocytic astrocytomas	130	1.31 (0.50, 3.42)	0.95 (0.32, 2.83)
Other gliomas	184	1.60 (0.77, 3.32)	1.57 (0.70, 3.51)
Other	697	1.27 (0.86, 1.88)	1.09 (0.72, 1.66)

Abreviations:
ALL: Acute Lymphoid Leukemia
AML: Acute Myeloid Leukemia
CNS: Central Nervous System.
[a] Models adjusted only by sex.
[b] Models adjusted by sex, degree of urbanization, availability of cantonal cancer registry, quintiles of socioeconomic status, and NO_2. In the fully adjusted analysis, one case of CNS tumors (glioma) was not included as its value for NO_2 was not available.
[c] HRs are obtained as the odds ratios from conditional logistic regression models fitted to nested case-control datasets matched on age (risk set sampling) and year of birth.

Table 4
Estimated population attributable fraction (PAF) and annual attributable cases of childhood cancer due to cumulative exposure to external background radiation in Switzerland.

	PAF[a] in % (95% CI[b])	Annual attributable cases[a] (95% CI[b])
Leukemia	32.2 (7.0, 49.3)	21 (5, 32)
CNS tumors	33.6 (5.5, 51.0)	17 (3, 26)

Abreviations:
CNS: Central Nervous System.
[a] Values are based on the exposure distribution and cancer incidence during the period 2000–2015 and on the dose coefficient from fitted models including a linear exposure term adjusted by sex, degree of urbanization, availability of cantonal cancer registry, quintiles of socioeconomic status, and NO_2.
[b] 95% CIs were obtained by repeating the calculations using the lower and upper confidence limits of dose coefficient instead of the point estimate.

the risks of lymphoma associated with exposure to ionizing radiation (Little et al., 2021; UNSCEAR, 2006). A recent pooled analysis of multiple cohorts found no evidence of an increased risks of lymphoma in relation to bone marrow dose, but did find indications of an excess risk for non-Hodgkin lymphoma when using lymphatic tissue dose (Little

et al., 2021).

The major strengths of our study are the nationwide cohort design, which maximizes sample size while minimizing the risk of selection bias, and the availability of exact geocodes of children's residential addresses at census time. A large amount of available airborne gamma-ray measurements provided a dense coverage of many heavily populated areas. The exposure model showed good performance in an internal validation with a coefficient of determination (R^2) of 0.75 in random cross-validation, and 0.40 in spatial cross-validation (Folly et al., 2021). Furthermore, we specifically modelled the depletion in the surface soil and the decay of ^{137}Cs contamination from the Chernobyl accident.

Our study did not include other important sources of radiation exposure in the general population such as domestic radon, diagnostic radiology, and ingested radionuclides, which may have confounded the associations estimated for external background radiation. However, this is unlikely for radon, as its decay products are mainly deposited in the respiratory tract and deliver the largest doses there. A previous study using overlapping data with the present study found no evidence of an association between estimated concentrations of domestic radon and childhood cancer risks (Hauri et al., 2013). A correlation between doses from ingested radionuclides and terrestrial gamma radiation is plausible as some proportion of drinking water and consumed agricultural food products come from local sources. A further limitation of this study is that exposure assessment was based only on outdoor measurements. Indoor exposure, where children spend most of their time, may differ considerably from outdoor exposure due to shielding effects and radiation stemming from building materials (UNSCEAR, 2008). Unfortunately, there was no sufficiently large dataset with indoor measurements of gamma radiation available. Also, modelling indoor exposure would have been further complicated by the lack of routine data on building materials. Another cause for potential exposure misclassification was our incomplete knowledge of residential histories. However, a recent study summarizing data from different European countries found that analyses based on a single address, which may introduce some measurement error, should still capture a large proportion of variability between individuals in exposure to background radiation (Nikkila et al., 2018).

Our study may have been affected by differential (by exposure) misclassification of the outcomes. Schindler et al. (2015) investigated completeness of the SCCR and found that children with brain tumors had been more likely to be missed in the registry than leukemias. The same study also found evidence of regional differences in the completeness of registration. We attempted to adjust for this by including a time-varying covariate indicating the presence of a general cancer registry in the canton of residence in our models. Lastly, not all eligible incident cases could be linked with the SNC, and some of the linked cases may have been falsely matched. This was another potential source of differential outcome misclassification that we could not account for.

The increased risk in childhood cancer was mainly driven by the risk observed for leukemia and CNS tumors. We cannot rule out bias from unmeasured confounding or measurement error. Indeed, restricting the analysis to children with fully known residential histories increased the strength of the association for leukemia but reduced it for CNS tumors. However, this shift in the observed associations could be due to other causes than the lower risk of exposure misclassification. Children in the restricted cohort were on average younger and followed-up for shorter periods. This could have differentially affected the analyses for leukemia and CNS tumors as cases of the former show a characteristic peak between ages 2–5 years (SCCR, 2019) whereas the latter are more evenly distributed across ages.

Regarding the risk of confounding, neither leukemia nor CNS tumors have known environmental risk factors apart from ionizing radiation. We found no indication of an association between exposure to domestic radon and childhood cancers in Switzerland in a previous study (Hauri et al., 2013) and thus did not include radon in the present analysis. We did consider exposure to traffic-related air pollution as a potential confounder for which there is support for an association with childhood leukemia from a recent systematic review and meta-analysis (Filippini et al., 2018) and a previous study in Switzerland (Spycher et al., 2015a, b). The included potential confounders had little effect on the results. However, we cannot exclude the possibility of residual confounding by other potential risk factors including other sources of radiation exposure such as diagnostic radiology or ingested radionuclides, for which we had no data available.

Assuming that the estimated dose-response relationships reflect a causal effect, our results suggest that external exposure to background radiation due to terrestrial gamma and cosmic radiation accounts for a considerable proportion of leukemia and CNS malignancies occurring in children.

5. Conclusion

Overall, these results provide further support that external natural background radiation may contribute to observed cancer rates in children, particularly of leukemia and CNS tumors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jenvrad.2021.106734.

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Ethics approval and consent to participate

All methods were performed in accordance with the Declaration of Helsinki and have been approved by an appropriate ethics committee. Ethics approval was granted through the Ethics Committee of the Canton

of Bern to the SCCR and the presented analyses on 22nd July 2014 (KEK-BE: 166/2014). According to the Ethics Committee of the Canton of Bern and national regulations, the need for informed consent from all participants was deemed unnecessary.

Availability of data and materials

The Swiss Childhood Cancer Registry and the Swiss National Cohort cannot be made publicly available for both legal and ethical reasons as this would compromise patient confidentiality and participant privacy.

Interested researchers may contact the corresponding author or the Swiss Childhood Cancer Registry (http://childhoodcancerregistry.ch/) via its online contact form for further information.

Individual data from different data sets were used for the construction of the SNC. All these data are the property of the Swiss Federal Statistical Office (SFSO) and can only be made available by legal agreements with the SFSO. This also applies to derivatives such as the analysis files used for this study. However, after approval of the SNC Scientific Board, a specific SNC module contract with the SFSO would allow researchers to receive analysis files for replication of the analysis. Data requests should be sent to Prof. Milo Puhan (chairman of the SNC Scientific Board, miloalan.puhan@uzh.ch).

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