Assessment of the findings from a childhood brain cancer cluster analysis in Switzerland

Report on behalf of the Federal Office of Public Health (FOPH)

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Disclaimer

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1 Summary

Konstantinoudis G et al (2020a) conducted a retrospective cohort study in Switzerland and reported that compared with the nationwide level the relative risk for childhood brain cancer was increased in the northern part of the canton of Zurich and in the Seeland region of the canton of Bern.

The Swiss Federal Office of Public Health (FOPH) has mandated the Swiss Center for Applied Human Toxicology (SCAHT) to establish an expert group to assess the strength and limitations of this study, including an assessment of the statistical methods used and an evaluation of the likelihood of the influence of other potential risk factors on the findings, that were not considered in the study. The expert group should also make recommendations for actions that could help verify the study's findings and/or explore the causes of the findings and better assess similar public health issues in the future.

SCAHT established a multidisciplinary expert group with experts from adult neuro-oncology, neurology and neurosurgery, pediatric oncology, environmental epidemiology and medical statistics. The expert group concluded that the authors conducted a well-designed epidemiological study and have carefully considered, collected, and adjusted for known confounding factors such as demographic factors and living circumstances. The novelty of the study is that small-scale analyses of disease clusters were performed on a 1 km^2 grid. Such small cluster analyses are suitable for detecting highly localized effects associated with pollutants from point sources. However, for rare diseases such as brain cancer in children, sample dispersion in small areas is very large, and there is a risk that even the smallest differences in case numbers between clusters will lead to false positives, i.e. suggesting the presence of a high-risk cluster when in fact it is just a random event. Therefore, the authors have applied Bayesian statistics which is the superior statistical analysis to smooth out chance fluctuation and avoid false positive results.

Overall, the expert group agrees that the reported spatial clusters should be interpreted with caution because the study shows small, if any, spatial variation and the effects were not very robust to the timing of residence assessment. Further uncertainty arises from the fact that there is high variability and relatively low interobserver agreement in the histopathologic evaluation of brain tumors. The grouping of different brain cancer subtypes into a single group by Konstantinoudis G et al (2020a) makes it difficult to draw reliable conclusions about the development of different brain cancer subtypes and their progression and it remains unknown whether the childhood brain cancer clusters represent an accumulation of different cancer subtypes with different causes. Also, there is no nationwide coverage for adolescents between 16 and 19 years of age in the childhood cancer registry (ChCR) which implies that cases will be collected differently in different areas. The expert group sees the added value of the study by Konstantinoudis G et al., 2020a as raising awareness of potentially problematic

sites and pointing public health experts to areas and public health issues that should be further explored.

Konstantinoudis G et al., 2020a developed hypotheses about the causes of the spatial brain cancer patterns and tested modelled ambient air concentration of nitrogen dioxide (NO_2), modelled exposure to background ionizing radiation, area-based socio-economic position (SEP), linguistic region, duration in years of general cancer registration in the canton and degree of urbanization as potential risk factors. With these covariates they could not fully explain the observed spatial differences in disease incidence. The expert group reviewed other potential risk factors described in the scientific literature and found that the only clearly established risk factors for childhood brain cancer are exposure to ionizing radiation and inherited genetic alterations. The expert group considers it unlikely that iatrogenic or diagnostic radiation explains the spatial childhood brain cancer clusters, but cannot rule out genetic changes as a cause because these are not systematically covered in the ChCR. Other factors with uncertain, controversial, or unproven effects on brain cancer risk, include acquired genetic changes from exposure to chemicals including pesticides. The expert group could not find clear evidence in the scientific literature that exposure to pesticides is causally related to brain cancer in children. Most epidemiological studies focus on adults and occupational exposures and on chemistry that is no longer marketed in Switzerland or will be banned soon. Also, personal exposure monitoring which is most relevant for human health risk assessment, was not available in most studies. The expert group acknowledges that Konstantinoudis G et al., 2020a have described an increased risk of brain cancer in children in two areas with intensive agriculture but notes that this could be a coincidence, as no increased risk has been described for other agricultural areas in Switzerland. The expert group argues that without further evidence of possible point source contamination in the affected clusters or prioritization of chemicals to be investigated based on hypotheses, it is not feasible to investigate chemical exposure as a risk factor because we are exposed to thousands of chemicals every day. The expert group emphasized that even if cluster-specific chemical contamination could be detected in the environment, retrospective individual exposure assessment would be difficult, if not impossible, due to lack of data.

Overall, the expert group does not see a need for further short-term measures because the spatial signal in the data is relatively weak and the cluster effects were not very robust to the timing of residence assessment. In the short term there is also no opportunity for further investigation of potential risk factors. Further research on this topic would require a larger patient cohort and accurate exposure information. Collecting prospective exposure data would require significant resources. This is costly, would require recruitment over several years, and might not provide timely results. Given the weak spatial signal in the data and the related uncertainties, it seems disproportionate to judge such an effort for only one specific research question. However, the situation would be different if there were a large-scale prospective cohort study including biobanking in Switzerland. With the systematic collection

of disease information and the collection of population-based biospecimens, one could also retrospectively detect chemicals in human body fluids and tissues and verify cause-and-effect relationships.

Therefore, the expert group recommends the implementation of large-scale human biomonitoring and, if pesticide exposure is a specific concern, the introduction of a pesticide reporting system to better manage public health related questions in the future. The expert group further recommends Swiss participation in large-scale international research projects to obtain sufficient number of patients, disease and exposure data for statistical analysis to overcome the fundamental challenges of researching a rare disease in small populations like Switzerland. As the causes for childhood CNS cancer are largely unknown, the expert group advises to strengthen further research of the pathomechanisms to better understand the etiology of childhood brain cancer. At a national level, the expert group recommends to evaluate whether it would be feasible to further optimize the ChCR. There seems to be room for optimization with respect to harmonization of language for cancer classification, systematic recording of hereditary genetic changes, additional state of the art molecular profiling, notably DNA methylation profiling and tracking of relocation patterns.

2 Abbreviations

Table 1: Abbreviations

AHS	Agricultural Health Study
ALL	Acute Lymphoblastic Leukemia
ChCR	Childhood Cancer Registry
CNS	Central Nervous System
FOPH	Federal Office of Public Health
HL	Hodgkin Lymphoma
NICER	National Institute for Cancer Epidemiology and Registration
NIH	US National Institutes of Health, National Cancer Institute
ISPM	Institute of Social and Preventive Medicine, University of Bern
OECD	Organization for Economic Co-operation and Development
RNCE	French national registry of childhood cancer
SCAHT	Swiss Centre for Applied Human Toxicology
SEP	Socio-Economic Position
SNC	Swiss National Cohort
TPH	Swiss Tropical and Public Health Institute

3 Introduction

Overall, cancer in children and adolescents is rare. However, cancer of the central nervous system (CNS), especially brain cancer, are the second most common type of cancer and the most common cause of cancer-related mortality in children. The causes of CNS cancer in children and adolescents are still largely unknown. They are thought to have a multifactorial etiology and many environmental risk factors are being discussed. However, the small number of cases makes causal attributions difficult and the exposure of patients to individual risk factors is difficult to verify. Life-threatening illnesses in children are of large public interest as children are particularly vulnerable and still developing.

In 2020, Konstantinoudis G et al., examined the spatial variation of CNS cancer in children in Switzerland and reported that the relative risk compared to the national level was highest for the north of the canton of Zurich and in Seeland region of the canton of Bern. The authors evaluated to which extent this variation can be explained by modelled ambient air concentration of nitrogen dioxide (NO_2), an air pollutant that is commonly used as an air quality indicator, modelled exposure to background ionizing radiation, area-based socio-economic position (SEP)[1], linguistic region, duration in years of general cancer registration in the canton or degree of urbanization. The selected risk factors considered in the analysis only partially explained the observed variation of CNS cancer suggesting that other environmental factors also play a role. Overall, the spatial variation in relative risk was small which suggests that there is not a strong spatial structure.

4 Terms of reference

The Swiss Federal Office of Public Health (FOPH) has mandated the Swiss Center for Applied Human Toxicology (SCAHT) to establish an expert group to assess the strength and limitations of the study by Konstantinoudis G et al, 2020, including an evaluation of the statistical analysis and an assessment of the likelihood of the influence of other, unmeasured factors on the findings. The expert group should search for similar clusters abroad and discuss possible implications of their overall findings for research, cancer registration, data management, new data collection, and legislation. The expert group should make recommendations for actions that could help verify the present findings and/or explore the causes of the findings. In addition, the expert group should suggest what is needed to be well prepared to evaluate similar new findings in the future.

[1] **SEP** Socioeconomic status or position is the social standing or class of an individual or group. It is often measured as a combination of education, income and occupation. Examinations of socioeconomic status often reveal inequities in access to resources, plus issues related to privilege, power and control https://www.apa.org/topics/socioeconomic-status

5 Methods

5.1 Expert group

SCAHT has established a multidisciplinary group of experts including epidemiologists to evaluate whether the study design and statistical methods are appropriate for the research question, and clinicians and toxicologists to assess the biological relevance of the reported differences in relative risk for CNS cancer (Table 1).

Table 1: Members of the expert group in alphabetical order

Dr. Lothar Aicher	Swiss Centre for Applied Human Toxicology (SCAHT)	Toxicologist
Dr. med. Emilie Le Rhun	University Hospital and University of Zurich, Department of Neurosurgery	Neurologist
Prof. PhD. Martin Röösli	Swiss Tropical and Public Health Institute (TPH)	Epidemiologist
Prof. Dr. med. Philippe Schucht	Inselspital Bern	Neurosurgeon
Prof. MD PhD. Ana Guerreiro Stücklin	University Children's Hospital Zurich	Pediatric Neurooncologist
Prof. Dr. med. Michael Weller	University Hospital and University of Zurich, Department of Neurology	Neurologist
Prof. Dr. Martin Wilks	Swiss Centre for Applied Human Toxicology (SCAHT)	Toxicologist

During the hybrid kick-off meeting, that was held on Friday 8th July, 2022 at the University Hospital Zurich, the most relevant questions for evaluation were identified and tasks were distributed among the experts according to their expertise. Subsequently, the SCAHT held one-to-one meetings with the respective expert group members, contacted additional experts at National Institute for Cancer Epidemiology and Registration (NICER) and at the Swiss Tropical and Public Health Institute (SwissTPH), consolidated expert opinions in a report draft, and circulated it among expert group members for further comments in two rounds.

6 Strength and weaknesses of the study by Konstantinoudis et al.

The expert group evaluated each aspect of this study including the study design, data collection, data analysis and used methods, and interpretation of the observed findings.

6.1 Study design

Konstantinoudis G et al., 2020a conducted a retrospective cohort study to investigate whether there is any spatial variation of childhood CNS cancer risk in Switzerland and whether risk can be explained by modelled ambient air concentration of NO_2, modelled exposure to background ionizing radiation, area- based socio-economic position (SEP), linguistic region, duration in years of general cancer registration in the canton or degree of urbanization. They included 902 children diagnosed with CNS cancer based on the location at birth and 1290 children based on the location of diagnosis. The study is the first investigation of small-area childhood cancer mapping using exact geocodes of place of residence. The authors used a 1

km^2 grid size as a compromise between high precision maps on the one hand, and data confidentiality considerations and reduction of computational burden on the other. Observation period was from 1985–2015. Children 0–15 years of age were included in the study. Cancer data were retrieved from the Swiss Childhood Cancer Registry and population data was available through the Swiss National Cohort (SNC).

→ The expert group acknowledges that spatial analyses of health outcomes as used by Konstantinoudis G et al., 2020a are an essential element of epidemiologic research. They can highlight sources of heterogeneity underlying spatial patterns in the health outcomes and consequently, reveal important public health determinants or etiologic clues. Early disease mapping studies were usually performed on a large geographic scale, using mostly international or regional comparisons. More recently, the availability of local geographically indexed health and population data, together with advances in computing and geographic information systems, has enabled the analysis of health data on a small geographic scale. Small-scale studies are easier to interpret because they are in principle less susceptible to ecologic bias from within-area heterogeneity of exposure, that is typically increasing with increasing area. Also, the heterogeneity of determinants other than area (co-variants) is expected to be less in small-scale studies.

→ The expert group agreed that the spatial disease mapping of childhood cancers using exact geocodes of place of residence as conducted by Konstantinoudis G et al., 2020a is better able to detect highly localized effects, such as those related to point source contaminations in the vicinity, than large-scale geographic studies at regional or country level (Richardson S et al., 2004). Small-scale disease cluster analyses can detect spatially limited hotspots that could be masked using a coarser grid. In a simulation study, the authors showed that spatial modelling based on exact geocodes more accurately identifies areas of higher risk compared to traditional disease mapping based on count data aggregated to small administrative areas (Konstantinoudis G et al., 2020b).

→ The expert group acknowledged that the influence of spatial changes on the development and progression of a disease cannot be traced with absolute certainty because children were only assigned to a specific risk area based on the date of birth and the date of diagnosis but relocation patterns in between were not considered. When Konstantinoudis G et al., 2020a used address at birth and not at diagnosis, they got in fact a somewhat different picture (online supplement of Konstantinoudis G et al., 2020a, tables S4 and S5) as illustrated by slightly different median and 95% credibility regions of risk ratios from spatial residence at diagnosis and birth for the six covariates tested.

→ Overall, the expert group noted that Konstantinoudis G et al., 2020a used a sample size that may be insufficient to approximate the true distribution of a rare disease like childhood CNS cancer being studied in small-scale areas.

6.2 Data collection

Konstantinoudis G et al., 2020a retrieved CNS cancer prevalence and incidence data from the Swiss Childhood Cancer Registry (ChCR) that collects residential addresses from the time of cancer diagnosis back to birth. The Cancer Registration Act (in effect from January 2020) mandates doctors and hospitals to report all cases of cancer diagnosed and treated in children and adolescents under 20 years of age to the national ChCR. The ChCR records new cases and data about the entire course of the disease and its treatment. To calculate population at risk, the authors used population counts within a specific area from the Swiss National Cohort (SNC). The SNC includes exact geocoded residential locations of all Swiss residents at the times of censuses (1990, 2000 and 2010–2015).

→ The expert group agreed that the two databases used by Konstantinoudis G et al., 2020a are most relevant and reliable and as complete as possible. Estimates suggest that the ChCR includes 91% of all childhood CNS cases for the period 1985-2009 but >95% for 1995-2009 (Konstantinoudis G et al., 2020a).

→ However, the expert group points out the following limitations of the databases that cause some uncertainty in the interpretation of the results of the spatial cluster analysis of childhood CNS cancer:

Firstly, in the ChCR, data coverage varies with time and depends on the duration in years of general cancer registration in the canton. The is particularly relevant for adolescents between 16 and 19 years of age, as they are often also treated in general oncology, especially when non pediatric cancers are involved. These have not been systematically reported to the pediatric cancer registry. Retrospectively, there is no nationwide coverage for this age group.

Secondly, there is generally high variability in the histopathological assessment of brain cancer and relatively poor interobserver agreement and the language used to classify the CNS cancer in the ChCR is assumed not to be entirely uniform making it difficult to draw reliable conclusions about the evolution of the different CNS cancer subtypes and their progression. Also, the ChCR includes benign and malignant CNS cancer in children, which are highly heterogeneous and have a variety of histopathologic entities. Thus, the observed cantonal accumulations represent cumulations of different CNS cancers.

Thirdly, the ChCR only records the place of birth and the place of residence at the time of diagnosis. Relocation patters after birth and before cancer diagnosis are not recorded and the influence of other places of residence on the development of cancer cannot be tracked.

Fourthly, the expert group criticizes that the assignment to a specific risk area based on addresses as recorded in the SNC may be subject to uncertainty. Addresses in the Konstantinoudis G et al., 2020a study were taken from the 1990, 2000, and 2010-2015 census data. If the time of birth and/or diagnosis of CNS cancer does not coincide exactly with these censuses, the location tracking might be inaccurate. The expert group notes

that an exact spatial assignment of cancer cases is only possible for census years. Relocation patterns of cancer patients in the years between censuses may dilute the spatial assignment of cancer cases to the place of residence.

6.3 Data analysis / statistics

Konstantinoudis G et al., 2020a performed small-scale disease cluster analyses, using a 1 km^2 grid. Such small cluster analyses are appropriate for detecting highly localized effects associated with point source contaminants. However, for rare diseases like childhood CNS cancer, the sampling variation in small areas is very large and there is a risk that even the smallest differences in case numbers between clusters can lead to false positive results i.e. suggesting the presence of a high-risk cluster, when actually this is not the case but only a random event. The expert group acknowledges that Bayesian statistics as used by Konstantinoudis G et al., 2020a is the superior statistical analysis to smooth out chance fluctuation and avoid false positive results. It performs well with sparse data and is commonly applied to remove background noise from data sets allowing important patterns to more clearly stand out and at the same time avoiding overinterpreting excesses arising by chance (Richardson S et al., 2004).

→ However, the expert group noted that it can nevertheless not be completely ruled out that the observed clusters are a product of chance. With small numbers of cases, the assumptions regarding underlying data distribution may not be completely fulfilled, which leads relatively easily to false positive results.

6.4 Data Interpretation

The expert group agrees that the reported spatial clustering of childhood CNS cancer in the north of the canton of Zurich and in Seeland region of the canton of Bern should be interpreted with caution for the following reasons:

→ The expert group notes that the Konstantinoudis G et al., 2020a study shows small, if any, spatial variation when comparing regions with national average. The relative CNS cancer risk of children living in the north of the canton of Zürich and in Seeland, compared to the Swiss national level is close to 1, indicating no difference to the national level. For childhood CNS cancer relative risk varied by location, from 0.82 to 1.23 indicating at most a 23% increase in the risk in certain grid cells compared to Switzerland as a whole.

→ The expert group states that the cluster effects observed in this study were not very robust to the timing of residence assessment. When Konstantinoudis G et al., 2020a use address at birth and not at diagnosis, they get in fact a somewhat different picture (online supplement of Konstantinoudis G et al., 2020a, tables S4 and S5) as illustrated by slightly

different median and 95% credibility regions of the posterior of risk ratios from spatial residence at diagnosis and birth for the six covariates tested.

→ The expert panel points out that with the current setting it is impossible to draw reliable conclusions about the causes of the six different clinical CNS cancer subtypes. CNS cancer is a heterogeneous disease that can be divided into different clinical subtypes that are grouped together based on similar prognosis and/or prediction. How many etiological subtypes exist for childhood CNS cancer that reflect a grouping with a common set of causes is unknown and can't be tracked in this setting. Konstantinoudis G et al., 2020a focused on the main clinical CNS cancer group (International Classification of Childhood Cancer main group III (ICCC3) because of the larger sample size compared to individual CNS cancer subtypes. It remains unknown whether the childhood CNS cancer clusters represent an accumulation of different cancer subtypes with different causes. The expert group suggested that a central pathology review also might help to better identify whether and which subtypes of CNS cancer show differential clustering.

→ The expert group notes that Konstantinoudis et al., 2020a found that the duration of general cancer registration in a canton can influence, at least to a small extent, the apparent spatial variation of childhood cancer cases based on the ChCR data. However, in the present case, the duration of the cancer registry could not explain the two spatial childhood CNS clusters. The Zurich cancer registry has existed for a long time (1980), but the Bern registry only since 2014, and the Fribourg registry since 2006. The expert group reasoned that the duration of a cantonal registry played a minor role for the registration of cancers in children aged 0-15 years (<16), as these had already been reported directly by the pediatric oncology clinics nationwide to the central pediatric cancer registry since the 1970s. The situation is somewhat different for cancer cases in adolescents because they have not been systematically reported to the pediatric cancer registry.

→ The expert group reiterates that the findings of Konstantinoudis G et al., 2020a describe a potential association between selected covariates and childhood CNS cancer but not a cause-and-effect relationship. The expert group acknowledged that Konstantinoudis G et al., 2020a reported weak evidence of an association of CNS cancer incidence with modelled exposure to background ionizing radiation which is in line with broader evidence as ionizing radiation is classified by the International Agency for Research on Cancer (IARC), as a category 1 carcinogen based on human evidence. However, it is a limitation of retrospective observational studies such as the one by Konstantinoudis G et al., 2020a that they can generally not be used to demonstrate causality but instead they can show associations. An association is a statistical relationship that describes a link between two variables (here childhood CNS cancer and exposure to any of the covariates) but does not imply causality. Associations can arise between variables in the presence and absence of a causal relationship whereas causation means that the exposure produces the effect. The

path from an association to an established causality is a long and difficult one but identifying cause-and-effect relationships typically starts with the identification of an association.

→ The expert group concludes that the added value of the study by Konstantinoudis G et al., 2020a is that it raises awareness for locations that appear potentially problematic and directs public health experts to areas and public health topics that should be further evaluated.

7 Risk factors for brain cancer

Cancer is primarily a genetic disease. It is caused by certain changes to genes that control how cells function, especially how they grow and divide. It is distinguished between inherited genetic changes and acquired genetic changes. Cancer-causing genetic changes can be acquired during one's lifetime, as the result of errors that occur as cells divide or from exposure to genotoxic substances that damage DNA and cause mutations that translate into cancer (American Cancer Society).
CNS cancer is thought to have a multifactorial etiology and many risk factors are being discussed. Konstantinoudis G et al., 2020a examined whether the spatial variation of risk for childhood CNS cancer can be explained by modelled ambient air concentration of nitrogen dioxide (NO_2), modelled exposure to background ionizing radiation, area-based socio-economic position (SEP), linguistic region, duration in years of general cancer registration in the canton or degree of urbanization. The authors reported weak evidence of an association of CNS cancer incidence with modelled exposure to background ionizing radiation and with SEP. In total, the six covariates considered explained 64% of the observed spatial variation for CNS cancer indicating that other factors are also play a role in CNS cancer ethology.

→ The expert group discussed other potential risk factors to childhood CNS cancer and reviewed the scientific literature to assess their relevance. According to the scientific literature, the only clearly demonstrated risk factors for brain cancer are ionizing radiation exposure and inherited genetic changes (Swiss Cancer Report 2021, American Cancer Society). Other factors with uncertain, controversial, or unproven effects on brain cancer risk, include acquired genetic changes from exposure to chemicals or biological stressors. In terms of spatially heterogeneously distributed environmental factors, exposure to industrial chemicals, including petroleum products and pesticides, occupational exposures of parents and infectious diseases in childhood are frequently mentioned.

7.1 Ionizing radiation

The etiology of brain cancer is poorly understood. The only confirmed environmental risk factor is exposure to ionizing radiation. At high doses, ionizing radiation can cause immediate damage to a person's body, including, at very high doses, death. At lower doses, ionizing

radiation can cause health effects such as cardiovascular disease and cataracts, as well as cancer. It causes cancer primarily because it damages DNA, which can lead to cancer-causing gene mutations. Children and adolescents can be more sensitive to the cancer-causing effects of ionizing radiation than adults because their bodies are still growing and developing. Also, children and adolescents usually have more years of life following radiation exposure during which cancer may develop (NIH).

The issue of increased risks of **cancer in the vicinity of nuclear facilities** has been studied extensively but no increased mortality from cancer, including brain and nervous system cancers has been shown (Williamson MR et al., 2021). More recently Williamson MR et al., 2021 examined brain cancer incidence rates in the USA in relation to the presence of nuclear reactors. The authors confirmed that brain cancer incidence rates were not associated with large nuclear power reactors that use nuclear energy in order to generate electricity but they found a positive association with smaller research facilities that use nuclear reactions for research which they could not explain. This association was not observed for young age groups (Williamson MR et al., 2021).

→ The expert group is not aware of childhood CNS cancer risk research for children and adolescents living in the vicinity of nuclear facilities in Switzerland. It also assumes that the case numbers for Switzerland would be too low to interpret any results.

Background ionizing radiation from terrestrial gamma and cosmic radiation has been considered by Konstantinoudis G et al., 2020a as a potential cause for CNS cancer in children. The authors found that the risk for childhood CNS cancer was increased for the predicted background ionizing radiation exposure (median 17% per standard deviation of radiation, i.e. per 60.2nSv/h).

→ The expert group acknowledged that Konstantinoudis G et al., 2020a reported weak evidence of an association of CNS cancer incidence with modelled exposure to background ionizing radiation which is in line with broader evidence as ionizing radiation is classified by the International Agency for Research on Cancer (IARC), as a category 1 carcinogen based on human evidence. However, the sum of all six covariates investigated by Konstantinoudis G et al., 2020a (see chapter 3), including background ionizing radiation could only explain 64% of the observed spatial variation for CNS cancer, suggesting that other factors also play a role.

Iatrogenic radiation exposure has not been considered by Konstantinoudis G et al., 2020a as potential covariate but is one of the few known risk factors for childhood brain cancer (Swiss Cancer Report 2021). The doses used are orders of magnitude in excess of what you would experience in the environment from natural radioactivity like rock or high-altitude radiation (Braganza MZ et al., 2012). According to the American Cancer Society today, most radiation-

induced brain cancer are caused by radiation to the head given to treat other cancer (iatrogenic radiation). They occur most often in people who received radiation to the brain as children as part of their treatment for leukemia. These brain cancer most often develop around 10 to 15 years after the radiation, but sometimes they might not appear until decades later (American Cancer Society).

→ The expert group considers it unlikely that iatrogenic radiation exposure is the cause of the observed clusters because in the affected CNS cancer patients no other cancer (e.g., leukemia) that would require therapeutic radiation have been identified.

Diagnostic radiation exposure has not been considered by Konstantinoudis G et al., 2020a as potential covariate but in a more recent study (Hauptmann M. et al., 2023), a significant dose-response relationship between CT scan-related radiation exposure and brain cancer in children and young adults is described.

→ The expert group argues that although diagnostic radiation exposure is more common than iatrogenic radiation exposure, it is lower in dose and it is not expected to cluster in a way it could explain the childhood CNS clusters. It can be assumed that the patients place of residence or birth does not coincide with the location of possible CT scans.

7.2 Cell phone use

Cell phones emit radiofrequency electromagnetic fields in the range of 700 MHz to 4 GHz, similar to WiFi and microwave ovens, radar, and satellite communication. Cell phones do not give off ionizing radiation, the type that can cause cancer by damaging the DNA inside cells. Cell phone use was not studied by Konstantinoudis G et al., 2020 but some studies have suggested a possible increased risk of brain cancer with cell phone use. However, most of the larger studies done so far have not found an increased risk, either overall or among specific types of cancer. Two large case-control studies, one of them including Swiss data, did not find evidence for a link between cell phone use and brain cancer in children (Castaño-Vinyals G et al., 2022).

→ The expert group acknowledges that cell phone use is one of the factors with controversial effects on brain cancer risk. The expert group agrees that there are very few studies of long-term use, and cell phones may not have been around long enough to fully determine the possible risks. It agrees that there remains some uncertainty to determine the possible risks of lifetime mobile phone use. The same is true of any possible higher risks in children, who are increasingly using cell phones. Cell phone technology also continues to change, and it is not clear how this might affect any risk. These risks are being studied, but it will probably be many years before firm conclusions can be made.

7.3 Inherited genetic changes

For all types of cancer diagnosed in all age groups genetic specialists estimate that between 5% to 10% are linked to an inherited mutated gene. Patients with familial cancer syndromes tend to have cancer at a higher frequency and earlier age of onset (Swiss Cancer Report 2021) and different gene mutations increase the risk of different types of cancer (Cancer Research UK). For brain cancer and combining all age groups, it can be said that in most people there is no family history of genetic changes and less than 1% develop in association with certain hereditary cancer diseases[2] (Swiss Cancer Report, 2021). For childhood brain cancer however, Zhang J. et al., 2016, reported that 8% of CNS cancer in children and adolescents are associated with cancer predisposition syndromes. Konstantinoudis G et al., 2020a have not considered inherited genetic changes as potential covariates.

→ The expert group acknowledges that in general the weak correlations between genetic changes and disease outbreaks, the unknown role of genetic polymorphisms and potential gene-environment-interactions are major challenges for the interpretation of inherited genetic changes. However, the expert group concluded that a genetic cause for the observed CNS cancer clusters in children cannot be excluded in principle.

→ In the specific case of Konstantinoudis G et al., 2020a, the expert group concluded that there are insufficient data to definitively determine whether heritable genetic alterations are causally related to higher cancer incidences observed in the two clusters because the ChCR does not systematically collect all family cancer history data, and it is likely that data in earlier years do not meet current standards.

7.4 Pesticides

The fact that Konstantinoudis G et al., 2020a found the greatest spatial dispersion in CNS cancer in children in areas of intensive agriculture may fuel public concern about an association between pesticide exposure and CNS cancer in children. This prompted the expert group to review the scientific literature for associations between pesticides and CNS cancer.
A recent meta-analysis of epidemiological studies suggests that agricultural exposures may play a role in the development of brain cancer (Gatto NM et al., 2021) but many other studies do not find a clear association between pesticide exposure and brain cancer (Lerro C et al., 2019). The most comprehensive prospective epidemiological study that investigates how agricultural lifestyle affects the health of farming populations is the Agricultural Health Study

[2] These diseases include Neurofibromatosis type 1 and 2 (NF1 and NF2), Li-Fraumeni syndrome, constitutional mismatch repair deficiency, Tuberous sclerosis, Von Hippel-Lindau syndrome, Turcot syndrome, Gorlin syndrome, Cowden syndrome (American Cancer Society, Tim Ripperger et al., 2017). Chromosomal abnormalities also confer an increased risk of cancer. Family members of children with cancer (siblings and offspring) may have an increased risk of cancer if they have any of the familial syndromes or genetic disorders mentioned (Swiss Cancer Report 2021).

(AHS). More than 89,000 US farmers and their spouses from Iowa and North Carolina have participated in the study since its start in 1993. Brain cancer incidence in AHS cohort compared with the general population has been evaluated several times and the findings were inconclusive. Excesses of brain cancer have been reported among agricultural workers, but findings are difficult to interpret because of the low number of cases and the unknown personal exposure. Excesses of childhood brain cancer have been associated with parental application of some pesticides in the AHS cohort but again findings are difficult to interpret because of the low number of cases and the unknown personal exposure.

→ The expert group recognizes that the effects of exposure to pesticides on brain cancer risk are controversial. The expert group could not find clear evidence in the scientific literature that exposure to pesticides is causally related to CNS cancer in children and the expert group is not aware of any studies that clearly demonstrate a causal relationship between exposure to pesticides and CNS cancer in children.

→ The expert group raises the concern that most epidemiologic studies have focused on adults and occupational exposures, and the relevance of these studies to the development of CNS cancer in children with a potentially shorter period of exposure than in adults remains unclear. Pediatric and adult brain cancer do differ in their incidence, histology / cancer type, molecular pathology, location, treatment strategies and outcome. The majority of adult brain cancer are metastatic lesions secondary to melanoma and lung or breast cancer whereas CNS cancer in children is in the majority primary cancer.

→ The expert group notes that the associations described in the literature were mostly obtained for chemistry that is known for its neurotoxic potential and is therefore no longer marketed in Switzerland as plant protection products such as aldrin, and ethyl dipropylthiocarbamate (Flower KB et al., 2004), or are still used as biocides but will be banned (dichlorvos) soon (FOPH website).

→ The expert group criticizes that personal exposure monitoring and biomonitoring which directly measure an individual's exposure as it occurs and are most relevant for human health risk assessment was not available in most studies described in the scientific literature. Instead, the different authors modelled individual environmental exposure based on questionnaires, geospatial databases or environmental sampling. Selective recall and incorrect classification of subjects with regard to their exposure status makes it difficult to estimate internal exposure and to interpret study results.

→ The expert panel concludes that comprehensive exposure data are needed for a clear understanding of the role of pesticides in childhood CNS cancer. It is not possible to measure these data retrospectively. Prospective collection would require considerable resources and could not provide timely results.

→ The expert group acknowledges that Konstantinoudis G et al., 2020a have described an increased risk of CNS cancer in children in two areas with intensive agriculture but notes that this could be a coincidence, as no increased risk has been described for other agricultural areas in Switzerland.

7.5 Chemicals

The expert group was asked to assess the likelihood of the influence of other unmeasured risk factors on the CNS cancer findings of Konstantinoudis G et al., 2020a and therefore discussed the role of chemical exposure beyond pesticides in a broader context. Every day we are exposed to hundreds or thousands of chemicals and chemical exposure is one of the factors with controversial effects on brain cancer.

Exposure to certain chemicals including petroleum products has been linked with an increased risk of brain cancer in some studies but not in others (American Cancer Society). Various components of vehicle emissions are carcinogenic, including diesel exhaust, benzene, 1,3-butadiene, and benzo(a)pyrene and several studies have investigated whether traffic-related pollution is associated with an increased risk of childhood cancer. The focus has been on leukemia, and specifically acute lymphoblastic leukemia (ALL), and cancer of the CNS. The published evidence is inconclusive. A nationwide study in Swiss children aged <16 years suggests that young children living close to highways are at increased risk of developing leukemia but little evidence of association was found for other cancer types (Spycher BD et al., 2015).

→ The expert group concludes that without further evidence of possible point source contamination in the affected clusters it will not be possible to follow up on individual chemicals as potential risk factors for the childhood CNS cancer clusters described by Konstantinoudis G et al., 2020a. Even if cluster-specific chemical contamination could be detected in the environment, retrospective individual exposure assessment would be difficult, if not impossible.

→ The expert group supports a Swiss Health Study based on a prospective large-scale cohort and biobank approach to meet such challenges in the future. Such an approach offers opportunities for systematic collection of disease information and exposure relevant factors including representative human biomonitoring for substances of interest. The measurement of chemicals in human body fluids and tissues, would provide direct information about human exposures to environmental stressors and would support human health risk assessment and the verification of a cause-and-effect relationship.

→ As the causes for childhood CNS cancer are largely unknown, the expert group advises to strengthen further research into the pathomechanisms to better understand the etiology

of childhood CNS cancer. New knowledge of how chemicals and other stressors induce CNS tumors must be generated and then aggregated in so-called OECD Adverse Outcome Pathways (AOP) (OECD AOP website). An AOP is an analytical construct that describes a sequential chain of causally linked events at different levels of biological organization (molecules, cells, tissues, organs, organisms) that lead to an adverse health effect. AOPs are the central element of a toxicological knowledge framework being built to support chemical risk assessment based on mechanistic reasoning. New in-vitro tests should then be developed for key events in the AOP that characterize the progression of the toxicity.

8 Childhood CNS cancer clusters in other countries

To find out whether or not spatial clustering of childhood cancer is a country-specific effect, the expert group investigated studies that performed parametric childhood CNS cancer mapping for other countries and identified a study in France and two in Florida, the latter refer to the same data source. Other studies examining the spatial distribution of childhood cancer generally show weak or no evidence of spatial clustering of CNS cancer (Armstrong BG, 1998, Goujon S et al., 2018, citation from Konstantinoudis G et al., 2020).

→ The expert group notes that overall, there is some evidence of spatial clustering of childhood CNS cancer in France and Florida, USA. However, a direct comparison of the different studies is difficult because different study designs, statistical approaches and spatial scales have been used. A detailed review of the individual studies would be needed to further clarify the relevance of the findings abroad for regulatory risk assessment.

8.1 France

Goujon S et al., 2018, recorded some spatial variation of childhood brain cancer on the larger departmental scale but on the smaller living zone scale the findings did not suggest a strong spatial structure. The authors investigated spatial variations of childhood cancer conducting a literature review and evaluating data on childhood cancer cases which were provided by the French national registry of childhood cancer (RNCE). They included 25’877 cases diagnosed over the period 2000-2014 in 0- to 14-year children living in mainland France at the time of diagnosis in the study. The spatial heterogeneity was tested, on two geographic scales (95 departments and 1960 living zones, and two spatial scan methods based on different software were used to detect clusters of cases). On the department scale, the study suggested some spatial heterogeneity for pilocytic astrocytomas, other gliomas and neuroblastomas and on a regional scale (Occitanie) for lymphoma. On the smaller living zone scale some spatial heterogeneity was observed for other embryonal cancer subgroups but those findings did not suggest a strong spatial structure and may be weak evidence. Because of its size, the department scale is appropriate to describe the overall spatial structure of childhood cancer but not to detect spatial heterogeneity on a finer scale or detect small

localized clusters. The living zone scale is of particular value for the description of childhood environments because, as the name suggests, the living zone constitutes an area in which people live and work.

8.2 Florida, USA

Lawson A and Rotejanaprasert C, 2014, reported evidence of spatial variation of brain cancer for cases 0–19 years old in Florida but the quality of the study must be further evaluated. The authors used 983 Florida zip code areas as geographical units and assessed pediatric brain cancer clusters in Florida for the years 2000–2010. They did not investigate whether they are associated with any covariates. Cancer data were available from the Florida Association of Pediatric Cancer Programs (FAPTP) childhood cancer registry (0–19 years old). The authors used two different statistical models to identify special clusters but did not adjust for confounding factors. They concluded that there is evidence of excess risk in a number of relatively dispersed zip codes across the state and some concentration of high excess risk in Polk, Lake, and Sumter counties (west of Orlando and north east of Tampa). These excesses are confirmed across the different statistical models used.

Raid WA et al., 2019 reported evidence of a spatial cluster of childhood brain cancer (0–19 years old) between Jacksonville and Orlando with a 60% higher cancer rate than the rest of Florida. The authors used Florida zip code areas as geographical units and assessed pediatric brain cancer clusters in Florida for the years 2000–2015. The focus was upon the three most widely seen pediatric cancer types in the USA: brain cancer, leukemia, and lymphomas. Cancer data were available from the Florida Association of Pediatric Cancer Programs (FAPTP) for 2000–2015. They investigated whether cancer clusters are associated with air pollution using an Environmental Protection Agency dataset on carcinogenic air pollution, the National Air Toxics Assessment (NATA). The authors used different statistical models to identify special clusters. For brain cancer rates, all three unadjusted models identified three statistically significant pediatric cancer clusters. When adjusted for age and sex, only one cluster with a 60% higher brain cancer rate than the rest of Florida remained, namely the area between Jacksonville and Orlando. When adjusted for age, sex, and for race, this cluster persisted but shifted in space. Another less likely cluster around Miami vanished after adjustment for race, implying that race explains the elevated brain cancer rates in this cluster. No apparent relationship between the atmospheric carcinogens included in the NATA files and pediatric brain cancer was identified.

9 Investigating CNS clusters in adults

Brain cancers are relatively rare for people of any age but they can occur in both children and adults although with a much higher incidence in adults (Greuter L et al., 2021). When considering only cancer that primarily arise in the brain, adult cancer are about ten times more common than those arising in children.

The expert group discussed whether it could be clarified whether the clusters observed by Konstantinoudis G et al. (2020) in children are also observed in adults and if such information would be helpful in elucidating the causes of the findings in children.

→ The expert group concluded that this would be a major task, made more difficult by the presumably higher mobility with increasing age and the patchy registration of cancer in adults. The duration of cancer registries and the completeness of cancer data varies considerably between cantons which would make spatial analysis complicated. The variability in the 13 cantonal cancer registries would already introduce some spatial structure in the Federal System of Cancer Registration. Also, it may take a certain time interval between exposure and development of a cancer, possibly limiting the examinations to certain entities, like those identified in the pediatric population. The expert group considered the chances of obtaining additional reliable information low.

→ Also, the expert group noted that the relevance of such an examination in adults to clarify findings in children and adolescents may be limited because the etiology of pediatric and adult brain tumors is largely different. The majority of adult brain cancer are metastatic lesions secondary to cancer such as melanoma and lung or breast cancer whereas metastatic lesions are very rare in children and information concerning the molecular biology of brain cancer strongly suggests that even apparently identical cancer types are different in adults and children (Bale and Rosenblum, 2022).

10 Conclusion

Konstantinoudis G et al., 2020a conducted a retrospective cohort study in Switzerland and observed two spatial clusters of increased relative risk for childhood CNS cancer compared with the nationwide level. The expert group concluded that Konstantinoudis G et al., 2020a conducted a well-designed epidemiological study and have carefully considered, collected, and adjusted for known confounding factors such as demographic factors and living circumstances. The novelty of the study by Konstantinoudis G et al. (2020a) is that they performed small-scale disease cluster analyses on a 1 km^2 grid. Such small cluster analyses are appropriate for detecting highly localized effects associated with point source contaminants. However, for rare diseases like childhood CNS cancer, the sampling variation in small areas is very large and there is a risk that even the smallest differences in case numbers between clusters can lead to false positive results giving the impression that we are dealing with a high-risk cluster, when actually this is not the case but only a random event. Bayesian statistics as used by Konstantinoudis G et al., 2020a is the superior statistical analysis to smooth out chance fluctuation and avoid false positive results.

Overall, the expert group agrees that the reported spatial clustering of childhood CNS cancer in the north of the canton of Zurich and in Seeland region of the canton of Bern should be interpreted with caution because the study shows small, if any, spatial variation when

comparing regions with national average and the cluster effects observed were not very robust to the timing of residence assessment. Further uncertainty arises from the fact that there is high variability and relatively low interobserver agreement in the histopathologic evaluation of brain tumors. The grouping of different CNS subtypes into a single group by Konstantinoudis G et al (2020a) makes it difficult to draw reliable conclusions about the development of different CNS cancer subtypes and their progression and it remains unknown whether the childhood CNS cancer clusters represent an accumulation of different cancer subtypes with different causes. The fact, there is no nationwide coverage for adolescents between 16 and 19 years of age in the ChCR also introduces some spatial structure in the ChCR. The expert group sees the added value of the study by Konstantinoudis G et al., 2020a as raising awareness of potentially problematic sites and pointing public health experts to areas and public health issues that should be further explored.

The expert group reviewed other potential risk factors for childhood CNS cancer described in the scientific literature but not investigated by Konstantinoudis G et al., 2020a and found that the only clearly established risk factors for childhood CNS cancer are exposure to ionizing radiation and inherited genetic alterations. The expert group considers it unlikely that iatrogenic or diagnostic radiation explains the spatial childhood CNS clusters, but cannot rule out genetic changes as a cause. Other factors with uncertain, controversial, or unproven effects on brain cancer risk, include acquired genetic changes from exposure to chemicals including pesticides. The expert group could not find clear evidence in the scientific literature that exposure to pesticides is causally related to CNS cancer in children. Most epidemiological studies focus on adults and occupational exposures and on chemistry that is no longer marketed in Switzerland or will be banned soon. Also, personal exposure or biomonitoring which are most relevant for human health risk assessment, was not available in most studies. The expert group acknowledges that Konstantinoudis G et al., 2020a have described an increased risk of CNS cancer in children in two areas with intensive agriculture but notes that this could be a coincidence, as no increased risk has been described for other agricultural areas in Switzerland. The expert group argues that without further evidence of possible point source contamination in the affected clusters or prioritization of chemicals based on hypotheses, it is not feasible to investigate chemical exposure as a risk factor because we are exposed to thousands of chemicals every day. However, even if cluster-specific chemical contamination could be detected in the environment, retrospective individual exposure assessment would be difficult, if not impossible, due to lack of data.

11 Recommendations from the expert group

To enhance our understanding of public health questions for which evidence is conflicting or absent the expert group makes the following recommendations:

→ **The expert group does not see a need nor an opportunity for further short-term measures**

because the spatial signal in the data is relatively weak, the cluster effects were not very robust to the timing of residence assessment and retrospective individual exposure assessment is not possible. Prospective collection would require considerable resources and could not provide timely results. Further research into the topic would need a large sample size and accurate exposure information. To obtain such information is costly and would need a prospective study with recruitment over numerous years. Given the weak spatial signal in the data, it seems disproportionate to make such an effort for only one specific research question. However, the situation would be different if there had been an existing large-scale prospective cohort study including biobanking in Switzerland (Probst-Hensch et al., 2022). If such a research platform is established, one could use existing data for further investigation.

→ **The expert group recommends the implementation of large-scale human biomonitoring** to better manage public health related questions in the future. The expert group supports a Swiss Health Study based on a prospective large-scale cohort and Biobank approach. This offers opportunities for systematic collection of disease information and exposure relevant factors including representative human biomonitoring for substances of interest. The measurement of chemicals in human body fluids and tissues, would provide direct information about human exposures to environmental stressors and would support human health risk assessment and the verification of a cause-and-effect relationship. For instance, one could re-analyze collected population-based biosamples to evaluate whether exposure to any chemicals of interest is increased in areas with elevated pediatric brain cancer rates. Another option would be to set up a targeted nested project in an efficient manner, and thus profiting from already collected data.

→ **The expert group recommends the introduction of a pesticide reporting system.** Pesticide exposure remains one of the factors with controversially discussed effects on brain cancer risk. To follow up on the hypothesis of an association between spatial clustering of childhood CNS cancer and pesticide exposure, one would need more detailed exposure data and a better linkage to disease data. A study conducted by the Bureau for Labor and Social Policy Studies (BASS) on behalf of SECO to examine existing surveillance systems for monitoring chronic effects of pesticides comes to similar conclusions (Gajta P and Zeyen P, 2020). The expert group agrees that the development of a nationwide pesticide reporting system that provides information on which pesticides are used where, when, and in what quantities could be a first step toward further clarifying the problem, but will not yet resolve the issue of personal exposure. This is because ambient monitoring might not capture all space and time variability in ambient concentrations including exposure peaks and therefore, might not reflect true individual exposure. Also,

establishing such a reporting system should include the possibility to link it with health data and other research data such as the Swiss Health Study.

→ **The expert group recommends further research collaboration.**
Among the fundamental challenges of researching a rare disease such as childhood CNS cancer is that not enough patient data are available for statistical analysis in small populations. Therefore, research should ideally be done in large-scale international projects to obtain sufficient number of patients, disease and exposure data for analysis. There are examples of successful research collaborations with Swiss participation such as a multicenter case-control study on mobile phone use and brain tumors in children and adolescents (Aydin D., et al., 2011) or the evaluation of the genetic and molecular bases of primary CNS cancer (Waszak, S., et al., 2020).
Also, existing patient data are not necessarily accessible for research. The extent to which existing legal frameworks in individual countries allow access to medical data for research purposes and for exchange with other countries must be examined.

→ **The expert group recommends further mechanistic research.**
As the causes for childhood CNS cancer are largely unknown, the expert group advises to strengthen further research of the pathomechanisms to better understand the etiology of childhood CNS cancer. New knowledge of how chemicals and other stressors induce CNS cancer must be generated and then systematically captured e.g., in Adverse Outcome Pathways (AOP) of the Organization for Economic Co-operation and Development (OECD) that describe a sequential chain of causally linked events that lead to an adverse health effect. New in-vitro tests should then be developed for key events in the AOP that characterize the progression of the toxicity.

→ **The expert group recommends further optimization of the ChCR.**
The need for high quality cancer data that can be linked to exposure data seems to be largely met with the establishment of the Swiss Cancer Registry. However, there seems to be room for further optimization (e.g., harmonization of language for cancer classification, systematic recording of hereditary genetic changes, additional state of the art molecular profiling, notably DNA methylation profiling, tracking of relocation patterns). The expert group recommends a feasibility study under the leadership of the ChCR to explore which additional parameters are likely to be most successful and whether the expected benefits justify additional costs.

→ **The expert group recommends to establish cross-functional networks.**
The expert group anticipates that the ongoing digital transformation of the Swiss healthcare system, combined with improved geographic information systems, will increase the availability of local, geographically indexed health and population data and trigger more spatial disease analyses. Public and political interest in such studies will

remain high. To respond appropriately and in a timely manner to future findings, the expert group recommends to establish a multidisciplinary scientific network involving toxicologists, epidemiologists, statisticians, clinicians and risk communication specialists.
The experience with the evaluation of the study by Konstantinoudis G et al., 2020a has shown that today it takes time to identify relevant experts across disciplines. This is mainly due to the fact that although the individual scientific disciplines are organized in networks, they are usually not interconnected and it is therefore time consuming to put together a team. Many professional associations maintain expert registries and as part of their registration experts must prove their qualifications. Therefore, these registers serve the purpose of quality assurance and it would make sense to have rapid access to the relevant professional registers in the future, in order to be able to contact qualified experts and to be able to put together a team independently in due time.

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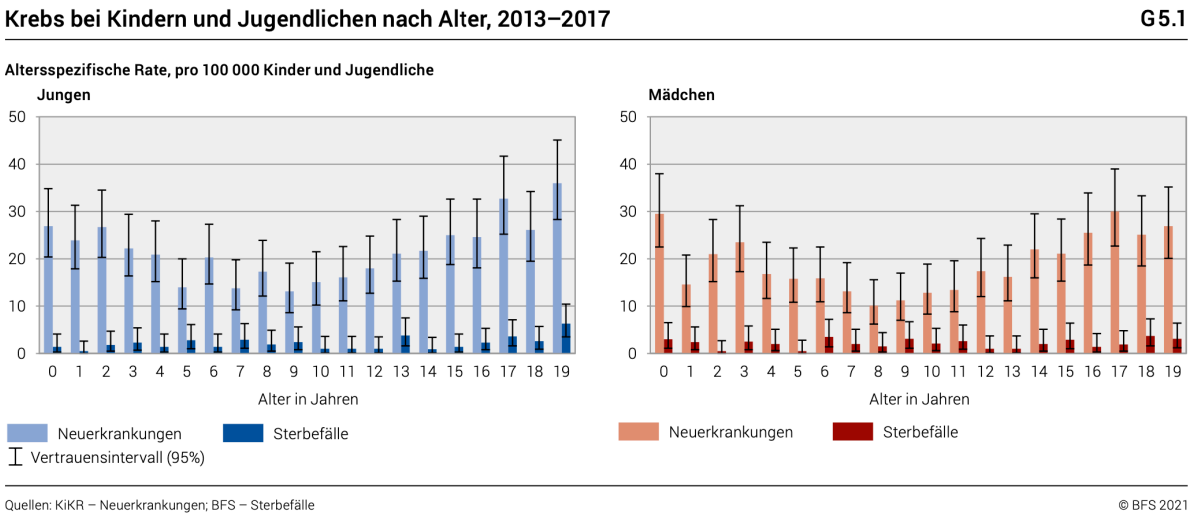
13 Appendix 1: Key epidemiologic indicators for CNS cancer in children

Cancer in children (0-14 years) and adolescents (15-19 years) is rare. Only about 4% of all cancer occur at the age of 0-19 years. Cancer occur more frequently in infants and 1–4-year-old children than in school-age children. In adolescents, the incidence slowly increases again, to rise further in adulthood. Most cancer types occur more frequently in boys than in girls (table 2).

Table 2: Childhood cancer incidence by age



13.1 CNS cancer incidence in comparison

Cancer of the central nervous system, especially brain cancer, are the second most common type of cancer (20.6%) (tables 3 and 4). In 2013-2017, a median of 355 boys and girls aged 0-19 years were diagnosed with CNS cancer annually in Switzerland (21 new diagnoses per 100'000 children and adolescents per year). During the first 20 years of life, approximately 430 per 100'000 boys and 380 per 100'000 girls are affected (Swiss Cancer Report 2021).
Only leukemia occur more frequently (24.5%), and the cases for lymphomas are slightly less (15.2%). Less frequent are soft tissue sarcomas (6.7%), which arise from degenerated soft tissue (fatty tissue, muscle tissue, tendons, connective tissue), and bone cancer (4.5%). Other cancer arise from embryonic tissue. These include germ cell cancer (6.2%), which can develop in the gonads but also at other sites such as the brain, peripheral nerve cell cancer (4.6%) from primitive nerve tissue, renal cancer (3.0%) from kidney tissue, retinoblastomas (1.3%) from cells of the retina, and liver cancer (< 1%) from tissue of the liver. The latter can arise in the gonads or in other locations, for example in the brain. Furthermore, other rare malignant cancer (< 1%) also exist in children and adolescents (tables 3 and 4) (Swiss Cancer Report 2021).

Table 3: Childhood cancer incidence by type of cancer

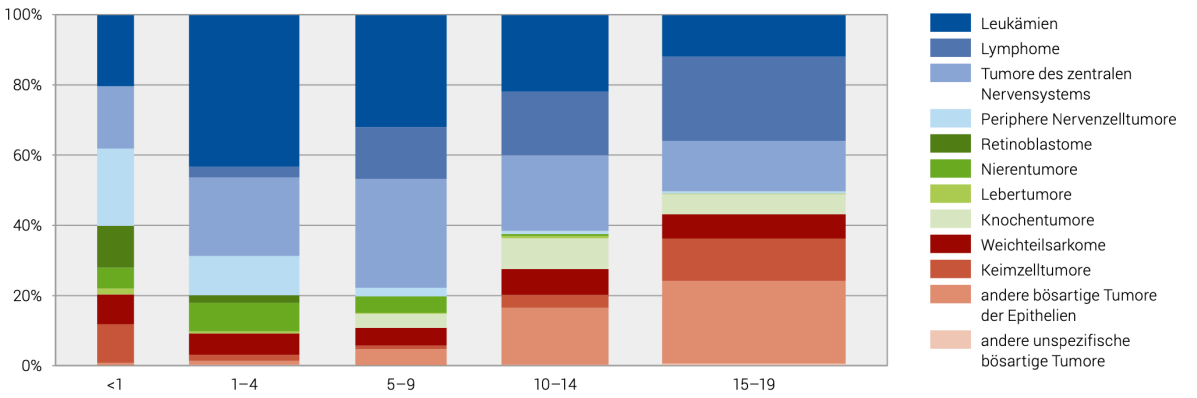
Krebs bei Kindern und Jugendlichen: Tumorgruppen nach Altersklasse, 2013–2017 **T5.1**

Tumorgruppen	Total		Alter bei Diagnose (Jahre)									
			<1		1–4		5–9		10–14		15–19	
	n	%	n	%	n	%	n	%	n	%	n	%
Leukämien	423	24,5	24	20,3	155	43	95	32	77	21,9	72	12
Lymphome	263	15,2	0	0	11	3,1	44	14,8	64	18,2	144	24
Tumore des zentralen Nervensystems	355	20,6	21	17,8	80	22	92	31	76	21,6	86	14,4
Periphere Nervenzelltumore	79	4,6	26	22	40	11	7	2,4	3	0,9	3	0,6
Retinoblastome	22	1,3	14	11,9	8	2,2	0	0	0	0	0	0
Nierentumore	52	3	7	5,9	29	8,1	14	4,7	2	0,6	0	0
Lebertumore	8	0,5	2	1,7	2	0,6	1	0,3	2	0,6	1	0,2
Knochentumore	77	4,5	0	0	0	0	12	4	31	8,8	34	5,7
Weichteilsarkome	115	6,7	10	8,5	22	6,1	15	5,1	26	7,4	42	7
Keimzelltumore	107	6,2	13	11	6	1,7	3	1	13	3,7	72	12
Andere bösartige Tumore der Epithelien	217	12,6	1	0,8	4	1,1	14	4,7	57	16,2	141	23,6
Andere unspezifische bösartige Tumore	5	0,3	0	0	1	0,3	0	0	1	0,3	3	0,6
Insgesamt	**1724**	**100**	**118**	**100**	**358**	**100**	**297**	**100**	**352**	**100**	**599**	**100**

Quelle: KiKR

Table 4: Childhood cancer incidence by type of cancer (bar chart)

Krebs bei Kindern und Jugendlichen: Tumorgruppen nach Altersklasse, 2013–2017 **G5.3**



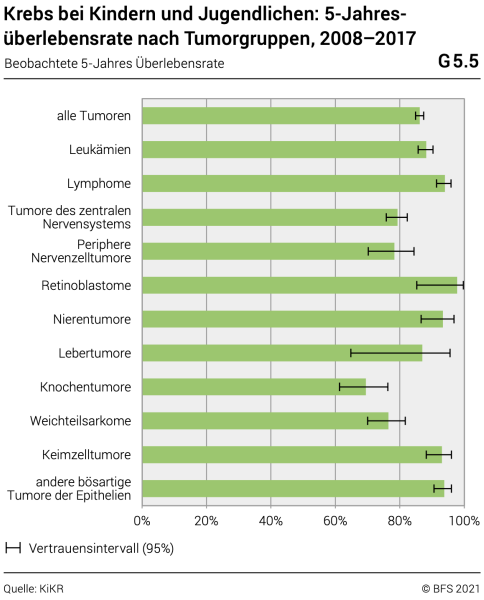
Die Flächen sind proportional zur Anzahl der Neuerkrankungen.

Quelle: KiKR

13.2 CNS cancer mortality, cure rates

The chances of cure for CNS cancer are less favorable. Compared with previous periods, the chances of cure for children and adolescents continued to improve over time. However, significant differences remain between the various diagnosis groups. The 5-year survival rate for children diagnosed between 2008 and 2017 was about 86%. The chances of cure are poorest for cancer of the central nervous system, advanced peripheral nerve cell cancer, bone cancer, and soft tissue sarcomas. The best cure rates are for lymphoma, retinoblastoma, renal cancer, and germ cell cancer (5-year survival over 90%). Leukemia follows with 88% cure rate (Swiss Cancer Report 2021). Despite this positive temporal trend, cancer remains the most common cause of disease-related death in children and adolescents.

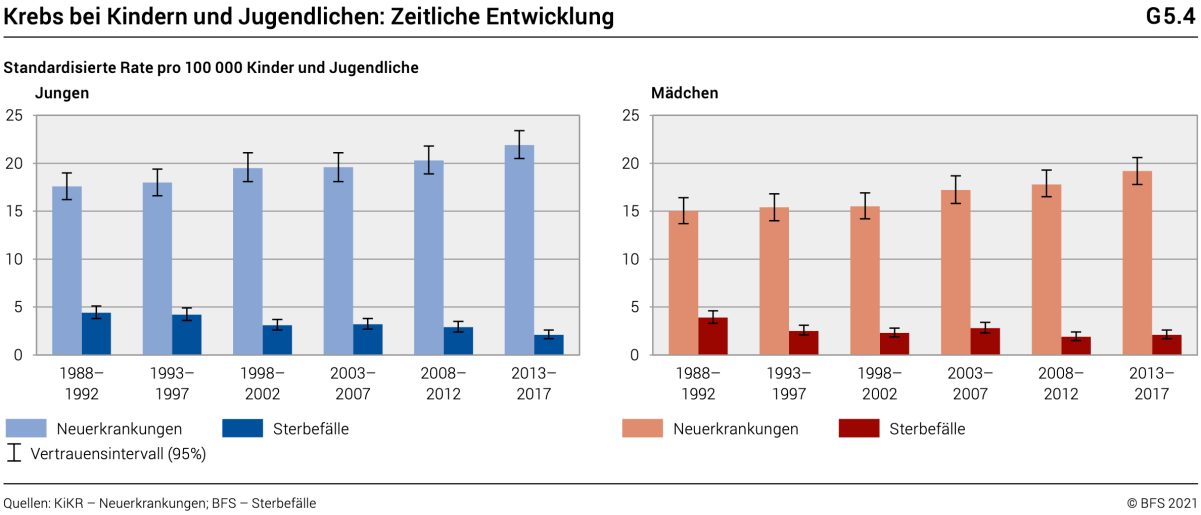
Table 5: Childhood cancer, 5-year survival rate by type of cancer



13.3 CNS cancer incidence - development over time

The increase in registered new childhood CNS cancer cases may reflect improved diagnostics. Since the early 1990s, a slight increase in registered new cancer cases for both boys and girls has been recorded. The estimated mean annual increase since 1998 is 0.8% for boys and 1.4% for girls (table 6). This increase may reflect an actual increase, particularly for leukemia. However, for other diagnoses, such as brain cancer, the increase could also reflect improved diagnostics. Mortality has been recorded with high completeness throughout the period. Mortality has steadily declined, from 4.2 per 100'000 per year (1988-1992) to 2.1 per 100'000 per year (2013-2017). This reflects improvements in therapy. Variations from period to period may be due to chance given the relatively small numbers of cases (Swiss Cancer Report 2021).

Table 6: Childhood cancer - development of time

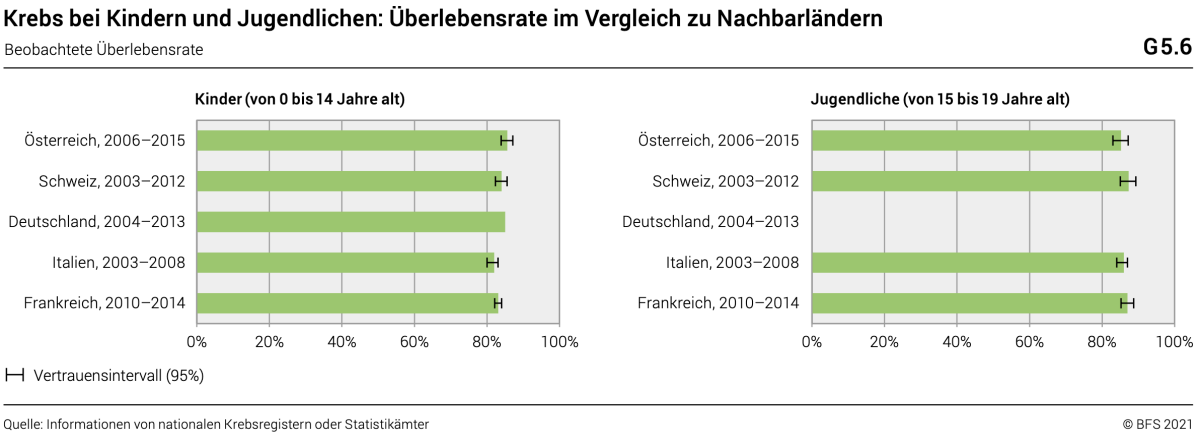


13.4 International comparisons

Swiss childhood cancer incidence and survival rates are comparable to neighbouring countries. In international comparisons, the incidence rate for cancer in children and adolescents aged 0-19 years in Switzerland (20.6 per 100’000 between 2013-2017) is similar to that in neighbouring countries: Germany 17 per 100’000 between 2009-2018 excluding 19-year-olds; Austria 17.8 per 100’000 between 2009-2018; Piedmont, Italy 16.6 per 100’000 between 1967-2011 (Swiss Cancer Report 2021, Lorez M et al., 2018).

Survival rates after childhood or adolescent cancer in Switzerland are also comparable to those in neighboring countries (Swiss Cancer Report 2021). While in the 1950s only about 20% of children with cancer survived, today more than 85% can be cured. The 5-year survival rate of Swiss children who developed cancer between 2008 and 2017 was about 86% (table 7).

Table 7: Survival rate in comparison to neighboring countries



13.5 International comparisons of childhood cancer clustering

For childhood cancer the general picture is inconsistent and for spatial clustering of CNS cancer only weak or no evidence has been described (Armstrong BG, 1998; McNally RJ and Eden TO, 2004; Goujon S et al., 2018).