# Ionizing and non-ionizing radiation and the risk of childhood cancer – illustrated with domestic radon and radio frequency electromagnetic field exposure

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## Summary


### Background

Childhood cancer is the second most common cause of death in children after accidents in developed countries. Children are exposed to many different environmental factors that are suspected to cause childhood cancer. With the exception of moderate and high-dose ionizing radiation, evidence for an association between environmental factors and childhood cancer is still limited. Among those factors with limited evidence for an association with childhood cancer rank the exposure to low-dose ionizing radiation as well as non-ionizing radiation. Low-dose ionizing radiation and non-ionizing radiation are ubiquitous.

In terms of low-dose ionizing radiation, it is distinguished between anthropogenic modified and radiation from natural sources where most of it is from natural sources. Natural ionizing radiation comprises cosmic rays from the atmosphere and terrestrial gamma radiation from radionuclides (Uranium-238, thorium-232, potassium-40) in rocks and soils. Natural ionizing radiation also comprises radiation from radon. Radon is a radioactive gas and a nuclide of a long radioactive decay chain, originating from Uranium-238. It emanates from soils and rocks into the atmosphere and buildings and decays again where its decay products emit alpha particles. Radon is the major sources of low-dose ionizing radiation exposure for humans. Radon is of concern as doses from radon gas to the red bone marrow were supposed to be high enough to cause childhood leukaemia. Gamma radiation can be considered as being of concern in terms of childhood cancer as it is able to traverse the human body.

Non-ionizing radiation comprises optical radiation and radiation from electromagnetic fields. The latter comprises radiation from extremely low-frequency electromagnetic fields (ELF-EMF) (high voltage power lines, electrical installations) and radiofrequency electromagnetic fields (RF-EMF) (broadcast transmitters, mobile phone base stations, mobile and cordless phones). Based on epidemiological studies on childhood leukaemia and central nervous system and brain tumours, the International Agency

for Research on Cancer (IARC) classified both ELF-EMF and RF-EMF as possibly carcinogenic.

Despite the assumption that ionizing and non-ionizing radiation might be associated with childhood cancer, only few studies on these issues have been published so far. Most of these studies are ecological or case-control studies. In ecological studies, data are analysed at an aggregated level and resulting associations cannot be interpreted at the individual level. Case-control studies are often faced with recall and selection bias. Past studies were further faced with difficulties in exposure assessment that further reduced the validity of these studies.

**Aims**

This dissertation is on ionizing and non-ionizing radiation and the risk of childhood cancer. Within this dissertation, we primarily aimed to assess whether there is an association between domestic radon exposure and childhood cancers. Within another analysis, we further aimed to investigate whether there is an association between low-dose ionizing gamma radiation and childhood cancers. This dissertation also comprises a section on non-ionizing radiation from far-field RF-EMF sources. The aim there was to assess whether there is an association between RF-EMF exposure from broadcast transmitters and childhood cancers.

**Methods**

Prospective census-based cohort designs were performed to assess the three subject areas, considered within this dissertation. All children, aged less than 16 years and living in Switzerland at the date of census 2000 (December 5$^{th}$ 2000) were considered for the analyses. Time at risk was set to begin at census and lasted until the date of diagnosis, death, emigration, a child's 16$^{th}$ birthday or until the end of the year 2008 whichever occurred first. In terms of non-ionizing radiation from far-field RF-EMF sources from broadcast transmitters, a further prospective cohort analysis was carried out, considering all children, aged less than 16 years and living in Switzerland between 1985 and 2008.

Exposure was assessed at baseline (date of census 2000) for each child's home address for the time of census 2000. For the analyses on RF-EMF exposure to broadcast transmitters and childhood cancer where a longer follow-up was considered, exposure at the time of diagnosis was considered.

For the exposure assessment, different methods were applied for the three subject areas. For the analyses on domestic radon exposure and childhood cancers, we assessed indoor radon exposure for each child's home address using a nationwide radon prediction model. We developed a regression model, based on almost 36,000 measurements, carried out all over Switzerland between 1994 and 2004. The model was validated in an independent dataset of almost 9,000 additional measurements which have not been used to develop the model. For the analyses on low-dose ionizing gamma radiation and childhood cancers, exposure assessment was based on digital maps with modelled and measured dose rates from outdoor gamma radiation. These were doses rates from terrestrial, cosmic and artificial ground radiation (Chernobyl fallout in the Southern part of Switzerland, 1986). For the analyses on RF-EMF exposure to broadcast transmitters and childhood cancers, field strengths were modeled by the Federal Office of Communications (OFCOM). The antenna height, the transmission duration, direction of the emissions and the local topography were considered for the field strengths models.

**Results**

Tectonic units, soil permeability, degree of urbanisation, housing type, building age and floor were identified as relevant predictors for the radon prediction model. The explained variance of the radon prediction model was 20%. Despite the low $R^2$, the exposure model was considered to be appropriate for predicting radon level exposure of the Swiss population. Comparison of predicted and measured radon values resulted in a Spearman rank correlation of 0.45 (95%-CI: 0.44, 0.46). Using a cut-off at the $90^{th}$ percentile, sensitivity was 31%, specificity 92%, Kappa coefficient 0.31 and the area under the ROC-curve was 0.73 (95%-CI: 0.72, 0.74). When validating the radon prediction model in the independent dataset, these values were almost the same as for the development set. This indicated that the model was robust and not overfitted.

Based on the radon prediction model, arithmetic mean radon concentration was estimated to be 85.7 Bq/m³ (range: 6.9-337.2 Bq/m³) for childhood cancer cases and 85.9 Bq/m³ (range: 0.7-490.1 Bq/m³) for the rest of the study population. In general, we found larger variations in predicted radon values between the different regions in Switzerland. We estimated higher radon values for households in the Alps and the Jurassic region than for the Central Plateau. We also estimated higher radon values for households in older buildings, in detached and farming houses and for households in lower floors. Despite relative high radon levels in Switzerland, no evidence was found that domestic radon exposure is associated with childhood cancers.

Based on the digital maps with dose rates from terrestrial, cosmic and artificial ground radiation, arithmetic mean of the estimated doses rates was 109 nSv/h (range: 55 - 247 nSv/h) for childhood cancer cases and 108 nSv/h (range: 55 – 383 nSv/h) for the rest of the study population. The analyses indicated a higher leukaemia risk (including acute lymphoblastic leukaemia (ALL)) for children who lived at the same address between 1995 and 2000. Compared with children exposed to a gamma radiation dose below the median (< 103 nSv/h), hazard ratios (HR) for children with exposure ≥ 90th percentile (≥133 nSv/h) were 2.02 (95%-CI: 1.05, 3.87) for all leukaemias and 2.59 (95%-CI: 1.22, 5.47) for acute lymphoblastic leukaemia. In contrast, no association between gamma radiation and childhood leukaemia (including ALL) was found for children who moved between 1995 and 2000. On the other hand, the analyses indicated elevated central nervous system (CNS) tumour risks for children who moved between 1995 and 2000.

Fifty one per cent of all children who were considered for the analyses on RF-EMF exposure to broadcast transmitters and childhood cancer lived within the modelled area at the time of census 2000. Arithmetic mean exposure in the whole study sample within the modelled area was 0.14 V/m where the maximum value was 9.77 V/m. The analyses indicated no association between RF-EMF from broadcasting and childhood leukaemia. On the other hand, increased CNS tumour risks were found in some of the analyses.

**Conclusions and Outlook**

The findings of our analyses, not indicating an association between domestic radon exposure and childhood cancers were consistent with past studies with estimated doses of domestic radon concentrations for different body organs. These dose estimations indicated that doses from domestic radon levels to organs other than the lung such as to the red bone marrow or the brain are too weak to increase cancer risks.

The results of the analyses on gamma radiation and childhood cancers strengthens the hypothesis that low dose ionizing gamma radiation might be relevant in terms of childhood leukaemia. The findings indicate that the same gamma radiation dose to the red bone marrow over a longer time period is probably necessary for gamma radiation to lead to childhood leukaemia. These results were found to be consistent with results from a recently published large case-control study from the United Kingdom. They also seem to be consistent with dose estimations for different organs and tissues. These dose estimations suggest that doses to the red bone marrow from gamma radiation are more important than from alpha radiation and that the red bone marrow is more sensitive to ionizing radiation than other body organs. In contrast, the elevated hazard ratios for CNS tumours for the group of children who moved between 1995 and 2000, were found neither to be consistent with dose estimations nor with the large case-control study, mentioned above. Hence, we drew the conclusion that there is currently little evidence for a causal relationship between background gamma radiation and CNS tumour risk in children.

The findings from the analyses on RF-EMF exposure from broadcast transmitters and childhood leukaemia were found to be consistent with two previous case-control studies and with results from animal, in-vitro and laboratory studies. Such studies did not find evidence for genotoxic effects from RF-EMF exposure. The findings indicating increased CNS tumours from RF-EMF exposure to broadcast transmitters on the other hand contradict results from a past case-control studies on RF-EMF exposure from broadcast transmitters and mobile phone base stations. In particular, they contradict results from the animal, in-vitro and in-vivo studies. In addition, one would also expect increased risk from use of wireless phones, which lead to substantially higher expo-

sure to the head. However, such an association was also not observed in a previous case-control study.

Although evidence for an association with childhood cancers was not found, domestic radon exposure is of public health relevance with regard to lung cancer in adults. Average domestic radon concentrations were found to be high in many regions in Switzerland. At the same time, a large part of the Swiss population (60%) is not aware of radon and its risk on health. Remedial actions in regions with high domestic radon values are therefore necessary. Second, a national campaign which promotes public knowledge on radon will be necessary.

The findings from the analyses on gamma radiation and childhood cancers indicate that gamma radiation is of public health relevance as well, especially when children are exposed to the same gamma radiation dose over a longer time period. Remedial actions are likewise necessary in order to reduce exposure from gamma radiation. Radionuclides that are responsible for terrestrial radiation are also found in building materials consisting of granitic and metamorphic stones. Therefore, a prevention strategy could consist in avoiding using building material with high content of such radionuclides.

In contrast to domestic radon exposure or exposure to background gamma radiation, statements on possible public health relevance concerning non-ionizing radiation of RF-EMF from broadcast transmitters are not yet possible. Within this thesis, it was suggested that a new prospective cohort or case-control study should be carried out in another country than Switzerland. This study should aim at investigating whether there is an association between RF-EMF from broadcast transmitters and CNS tumours in children. Analogous to our study, such a study should be based on census data and cancer cases from registries and modeled field strengths. This would allow seeing whether results from such a study are consistent with the findings from our study. This would possibly allow a statement on a public health relevance concerning non-ionizing radiation from broadcast transmitters.

# Zusammenfassung


## Hintergrund

In den Industrieländern geht jeder zweite Todesfall bei Kindern nach Verkehrsunfällen auf Krebs zurück. Kinder sind verschiedenen Umweltfaktoren ausgesetzt, die kanzerogen verdächtig sind. Mit Ausnahme von mittlerer und hoch-ionisierender Strahlung ist die Beweislage bezüglich eines Zusammenhangs zwischen verschiedenen Umweltfaktoren und Kinderkrebs noch immer dürftig. Darunter fällt die Exposition durch niedrig dosierte ionisierende Strahlung aber auch durch nicht-ionisierende Strahlung.

Niedrig dosierte ionisierende und nicht-ionisierende Strahlung sind in der Umwelt ubiquitär. Dabei ist bei der niedrig dosierte ionisierende Strahlung zwischen natürlicher und anthropogen veränderter Strahlung zu unterscheiden. Natürlich ionisierende Strahlung bildet den Hauptbestandteil der niedrig dosierten ionisierenden Strahlung. Die natürliche ionisierende Strahlung umfasst kosmische Strahlung aus der Luft und terrestrische Gammastrahlung von Radionukliden (Uran-238, Thorium-232, Kalium-40) in Gesteinen und Böden. Natürlich ionisierende Strahlung umfasst auch Strahlung von Radon. Radon ist ein Edelgas, welches durch den Zerfall von Uran im Boden entsteht. Radon diffundiert aus dem Boden und Gesteinen in die Atmosphäre sowie in Gebäude und zerfällt wieder, wobei seine Zerfallsprodukte Alphastrahlen emittieren. Bezüglich der Exposition des Menschen gegenüber niedrig-dosierter ionisierender Strahlung macht Radon den Hauptbestandteil aus. Radon ist darum besorgniserregend, weil angenommen wurde, dass die Dosis von Radon für das blutbildende Knochenmark hoch genug wäre, um Kinderleukämie zu verursachen. Gammastrahlung kann darum in Zusammenhang mit Kinderkrebs als besorgniserregend angesehen werden, weil Gammastrahlen den ganzen Körper durchdringen können.

Nicht-ionisierende Strahlung umfasst neben optischer Strahlung solche von elektromagnetischen Feldern, d.h. von niederfrequenten (Hochspannungsleitungen, elektrische Installationen) und hochfrequenten elektromagnetischen Feldern (HF-EMF) (Radio- und Fernsehsendestationen, Mobilfunkbasisstationen, Mobil- und Schnurlostelefonen). Basierend auf epidemiologischen Studien zu Kinderleukämie und Hirntumo-

ren sowie Tumoren des zentralen Nervensystems klassierte die Internationale Agentur für Krebsforschung (IARC) elektromagnetische Strahlung von nieder- und hochfrequenten elektromagnetischen Feldern als möglicherweise kanzerogen.

Obwohl angenommen wird, dass niedrig dosierte ionisierende Strahlung als auch nicht-ionisierende Strahlung in Zusammenhang mit Kinderkrebs stehen, liegen dazu nur wenige Studien vor. Die meisten Studien sind ökologische Studien oder Fall-Kontrollstudien. In ökologischen Studien wird der Zusammenhang zwischen Exposition und Gesundheit auf aggregierter Ebene durchgeführt, so dass Rückschlüsse auf Individuen nicht möglich sind. Fall-Kontrollstudien sind oft mit Recall- und Selektionsbias konfrontiert. Schwierigkeiten bestanden in der Vergangenheit auch in der Expositionsabschätzung, was die Aussagekraft vergangener Studien zusätzlich reduzierte.

**Ziele**

Diese Dissertation handelt von ionisierender und nicht-ionisierender Strahlung und Kinderkrebs. Im Rahmen dieser Dissertation wollten wir in erster Linie untersuchen, ob es einen Zusammenhang zwischen häuslicher Radonkonzentration und Kinderkrebs gibt. Innerhalb einer weiteren Analyse sollte zudem untersucht werden, ob es einen Zusammenhang zwischen niedrig dosierter ionisierender Gammastrahlung und Kinderkrebs gibt. Diese Dissertation widmet aber auch einen Abschnitt der nicht-ionisierenden Strahlung von HF-EMF Fernfeldquellen. Dabei sollte untersucht werden, ob es einen Zusammenhang zwischen der Exposition gegenüber HF-EMF-Strahlung von Radio- und Fernsehsendestationen und Kinderkrebs gibt.

**Methoden**

Wir führten für die in dieser Dissertation berücksichtigten drei Themenbereiche zensus-basierte prospektive zensusbasierte Kohortenstudien durch. In den Analysen wurden alle Kinder berücksichtigt, die zum Zeitpunkt des Zensus 2000 (5.12.2000) jünger als 16 Jahre alt und wohnhaft in der Schweiz waren. Die Beobachtungszeit begann jeweils am Zeitpunkt des Zensus 2000 und dauerte bis zum Zeitpunkt der Diagnose, des Todesfalls eines Kindes, bis zum Auswanderungsdatum, dem Zeitpunkt, an welchem ein Kind 16 Jahre alt wurde oder bis Ende 2008, was immer sich zuerst ereigne-

te. Bezüglich der Strahlung von Radio- und Fernsehsendestationen wurde zusätzlich eine prospektive Kohortenanalyse durchgeführt, in der alle Kinder, die jünger als 16 Jahre alt waren und zwischen 1985 und 2008 in der Schweiz wohnhaft waren, berücksichtigt wurden.

Die Exposition wurde jeweils für den Zeitpunkt des Zensus 2000 für jede einzelne Wohnadresse abgeschätzt. Bei der Analyse zu den Sendestationen mit der längeren follow-up Periode wurde die Exposition zum Zeitpunkt der Diagnose berücksichtigt.

Bezüglich der Expositionsabschätzungen kamen für die drei Themenbereiche unterschiedliche Methoden zur Anwendung. Für die Analysen zur häuslichen Radonkonzentration und Kinderkrebs schätzten wir die häusliche Radonexposition für jede einzelne Wohnadresse anhand eines Prädiktionsmodelles ab. Dabei entwickelten wir ein Regressionsmodell, das auf beinahe 36'000 Messungen basierte, die zwischen 1994 und 2004 in der ganzen Schweiz durchgeführt wurden. Das Modell wurde in einem unabhängigen Datenset, das fast 9,000 zusätzliche Messungen umfasste, die nicht für die Modellentwicklung verwendet wurden, validiert. Für die Abschätzung der Exposition durch Gammastrahlen lagen uns Karten vor, in denen die Strahlendosis von terrestrischer, kosmischer sowie von künstlicher Strahlung (Tschernobyl-Fallout in der Südschweiz von 1986) ausserhalb von Gebäuden gemessen und modelliert wurde. Für die Expositionsabschätzung durch die Strahlenbelastung durch Radio- und Fernsehsender lagen uns Feldstärkenmodelle seitens des Bundesamtes für Kommunikation (BAKOM) vor. In diesen Feldstärkenmodellen wurden die Antennenhöhe, Transmissionsdauer, die Strahlungsrichtung sowie die lokale Topographie berücksichtigt.

**Resultate**

Für das Prädiktionsmodell wurden geologische Einheiten, die Bodentextur, Verstädterungsgrad, Gebäudetyp und Gebäudealter sowie das Geschoss, auf denen die Haushalte zu liegen kamen, als relevante Faktoren identifiziert. Das Modell erklärte 20 % der Varianz. Obwohl das Bestimmtheitsmass tief war, befanden wir das Modell als gut für die Vorhersage von Radonwerten für die Schweizer Bevölkerung. Denn ein Vergleich zwischen gemessenen und vorhergesagten Werten lieferte eine Spearman Kor-

relation von 0.45 (95 %-KI: 0.44, 0.46). Bei Verwendung des 90. Perzentils als Trennpunkt betrug die Sensitivität 31%, die Spezifizität 92%, der Kappa Koeffizient 0.31 und der Wert für die Fläche unter der ROC-Kurve 0.73 (95 %-KI: 0.72, 0.74). Eine Anwendung des Prädiktionsmodelles auf das Validierungsdatenset zeigte, dass diese Werte beinahe dieselben wie im Development-Datenset waren. Das zeigte, dass das Prädiktionsmodell robust und nicht überangepasst war.

Anhand unseres Radonmodells schätzten wir, dass Kinder mit Krebs einer durchschnittlichen Radonkonzentration (arithmetisches Mittel) von 85.7 Bq/m³ (Spannweite: 6.9 – 337.2 Bq/m³) ausgesetzt waren. Für alle übrigen Kinder betrug dieser Wert 85.9 Bq/m³ (Spannweite: 0.7 – 490.1 Bq/m³). Generell stellten wir grosse Unterschiede in der Exposition zwischen den verschiedenen Regionen in der Schweiz fest. Wir schätzten höhere Radonwerte für Haushalte in der alpinen Region und der Juraregion als für solche im Schweizerischen Mittelland. Wir schätzten auch höhere Werte für Haushalte in ältere Gebäude, für solche in Einfamilien- und Bauernhäuser sowie für Haushalte in tiefer gelegenen Stockwerken. Trotz der relativen hohen Radonbelastung in der Schweiz zeigten unsere Analysen keinen Zusammenhang zwischen häuslicher Radonkonzentration und Kinderkrebs auf.

Anhand der Dosiskarten zur Gammastrahlung schätzten wir, dass Kinder mit Krebs einer durchschnittlichen Dosis (arithmetisches Mittel) von 109 nSv/h (Spannweite: 55 – 247 nSv/h) ausgesetzt waren. Für alle übrigen Kinder betrug dieser Wert 108 nSv/h (Spannweite: 55 – 383 nSv/h). Unsere Analysen zeigten, dass Kinder, die zwischen 1995 und 2000 am gleichen Wohnort wohnten, ein erhöhtes Leukämierisiko (inklusive akute lymphatische Leukämie) aufwiesen. Verglichen mit Kindern, welche eine Gammadosis unter 103 nSv/h (< Median) ausgesetzt waren, betrug die Hazard Ratio für die 10% am höchsten exponierten Kinder (≥ 133 nSv/h) 2.02 (95%-KI: 1.05, 3.87) für alle Leukämieerkrankungen und 2.59 (95%-KI: 1.22, 5.47) für akute lymphatische Leukämie. Wir fanden hingegen keinen Zusammenhang zwischen Gammastrahlung und Kinderleukämie (inklusive akute lymphatische Leukämie) bei Kindern, welche zwischen 1995 und 2000 umgezogen sind. Hingegen fanden wir erhöhte Risiken für Tu-

more des zentralen Nervensystems (ZNS-Tumore) bei Kindern, welche zwischen 1995 und 2000 umgezogen sind.

51% aller Kinder, welche für die Analyse zur HF-EMF Belastung von Radio- und Fernsehstationen berücksichtigt wurden, wohnten innerhalb des modellierten Gebietes zum Zeitpunkt des Zensus 2000. Diese Kinder waren im Durchschnitt (arithmetisches Mittel) einer Feldstärke von 0.14 V/m ausgesetzt, wobei der Maximalwert 9.77 V/m betrug. Die Analysen zeigten keinen Zusammenhang zwischen HF-EMF Belastung von Radio- und Fernsehstationen und Kinderleukämie auf. Innerhalb von einzelnen Analysen wurden aber erhöhte Risiken für Tumore des zentralen Nervensystems geschätzt.

**Schlussfolgerungen und Ausblick**

Die Resultate unserer Analysen, welche keinen Zusammenhang zwischen häuslicher Radonkonzentration und Kinderkrebs zeigten, standen in Einklang mit vergangenen Studien, welche Dosen von häuslicher Radonkonzentration für verschiedene Körperorgane abschätzten. Diese Dosisabschätzungen zeigten, dass die Radondosis für andere Körperorgane als für die Lunge wie z.B. das blutbildende Knochenmark oder das Gehirn zu gering sind, um das Krebsrisiko zu erhöhen.

Die Resultate zur Gammastrahlung und Kinderkrebs stärken die Hypothese, dass niedrig-dosierte ionisierende Gammastrahlung relevant in Zusammenhang mit Kinderleukämie ist. Die Resultate zeigen, dass möglicherweise dieselbe Dosis an Gammastrahlung für das blutbildende Knochenmark über einen längeren Zeitraum notwendig ist, damit Gammastrahlung zu Kinderkrebs führen kann. Diese Resultate stehen in Einklang mit einer kürzlich erschienen, grossen Fall-Kontrollstudie aus Grossbritannien. Sie stehen auch in Einklang mit Dosisabschätzungen für verschiedene Körperorgane. Diese Dosisabschätzungen zeigen, dass die Dosis durch Gammastrahlung für das blutbildende Knochenmark viel höher ist als durch Radon und dass das blutbildende Knochenmark gegenüber ionisierender Strahlung empfindlicher ist als andere Körperorgane. Hingegen stehen die Resultate, welche ein erhöhtes Risiko für

ZNS Tumore bei Kindern zeigten, die zwischen 1995 und 2000 umgezogen sind, in Widerspruch zu Dosisabschätzungen als auch mit der grossen Fall-Kontrollstudie. Wir kamen deswegen zur Schlussfolgerung, dass momentan wenig Evidenz für einen kausalen Zusammenhang zwischen Gammastrahlung und ZNS Tumoren bei Kindern besteht.

Die Resultate zur nicht-ionisierender HF-EMF Strahlung von Radio- und Fernsehsendestationen und Kinderleukämie standen in Einklang mit zwei vergangenen Fall-Kontrollstudien sowie mit Daten aus Tierversuchs-, in-vitro und in-vivo Studien. Letztere fanden keinen Beweis für genotoxische Effekte in Zusammenhang mit HF-EMF Strahlung. Die gesehenen erhöhten Risiken für Tumore des zentralen Nervensystems stehen hingegen im Widerspruch zu Resultaten vergangener Fall-Kontrollstudien zur Strahlung von Radio- und Fernsehstationen und Mobilfunkbasisstationen. Unsere Resultate stehen insbesondere zu den Tierversuchs- und in-vitro und in-vivo Studien in Widerspruch. Zudem würde man auch erhöhte Risiken für Tumore des zentralen Nervensystems durch die Exposition von Schnurlostelefonen erwarten, da dort der Kopf einer viel höheren Exposition ausgesetzt ist, was aber in einer vergangenen Fall-Kontrollstudie ebenfalls nicht bestätigt werden konnte.

Obwohl wir keinen Zusammenhang zwischen häuslicher Radonkonzentration und Kinderkrebs fanden, stellt die häusliche Radonexposition der Bevölkerung in der Schweiz ein Public Health Problem dar. In vielen Regionen der Schweiz ist die häusliche Radonkonzentration hoch und es wurde ein Zusammenhang zwischen häuslicher Radonkonzentration und Lungenkrebs bei Erwachsenen gefunden. Daher sind bauliche Massnahmen in Regionen mit hoher Radonkonzentration angebracht. Gleichzeitig hat man festgestellt, dass sich ein grosser Teil der Schweizer Bevölkerung (60%) diese Problematik nicht bewusst ist und damit eine Aufklärungskampagne seitens des Staates notwendig wäre.

Die Resultate unserer Untersuchungen zur Gammastrahlung zeigen, dass diese ebenfalls ein Public Health Problem darstellt, insbesondere wenn Kinder über einen längeren Zeitraum derselben Dosis an Gammastrahlung ausgesetzt sind. Auch hier wären

bauliche Massnahmen notwendig, um die Exposition von Gammastrahlung zu minimieren. Radionuklide, welche für die terrestrische Strahlung verantwortlich sind, kommen auch in Baumaterial, das aus Granit und metamorphem Gestein besteht, vor. Eine mögliche Präventionsmassnahme könnte darin bestehen, dass auf Baumaterial, das einen hohen Anteil an solchen Radionukliden enthält, verzichtet wird.

Im Gegensatz zur häuslichen Radonexposition oder zur Exposition gegenüber Gammastrahlung sind Aussagen darüber, ob hochfrequente elektromagnetische Strahlungen von Radio- und Fernsehsendern public health relevant sind, noch nicht möglich. Innerhalb dieser Dissertation wurde vorgeschlagen, eine neue prospektive Kohortenstudie oder Fall-Kontrollstudie in einem anderen Land als in der Schweiz durchzuführen. Diese Studie soll zum Ziel haben, zu untersuchen, ob es einen Zusammenhang zwischen hochfrequenten elektromagnetischen Strahlungen von Radio- und Fernsehsendern und ZNS-Tumoren bei Kindern gibt. Analog zu unserer Studie sollte eine solche Studie auf Zensusdaten und registerbasierten Krebsfällen basieren. Dies würde es erlauben, zu sehen, ob Resultate von einer solchen Studie konsistent mit denjenigen von unserer Studie sind. Dies würde möglicherweise ein Public Health Startement bezüglich nicht-ionisierender Strahlung von Sendestationen erlauben.

# List of abbreviations and definitions

**Abbreviations**

| | |
|---|---|
| AIC | Akaike's information criterion |
| ALL | Acute lymphoblastic leukaemia |
| AML | Acute myeloblastic leukaemia |
| BEIR | Biological Effects of Ionizing Radiation |
| BIC | Bayesian information criterion |
| Bq/m³ | Becquerel per cubic metre |
| CLL | Chronic lymphoid leukaemia |
| CML | Chronic myeloid leukaemias |
| CNS tumours | Central nervous system tumours |
| DoReMi | Low Dose Research towards Multidisciplinary Integration |
| EMF | Electromagnetic field |
| ELF | Extremely low frequency |
| ELF-MF | Extremely low frequency magnetic fields |
| GHz | Gigahertz (= 1,000,000,000 Hz) |
| Gy | Gray (unit for the absorbed dose) |
| HR | Hazard ratio |
| Hz | Hertz |
| IARC | International Agency for Research on Cancer |
| kHZ | Kilohertz (= 1,000 Hz) |
| mSv | MiliSievert (= 0.001 Sv) |
| $NO_2$ | Nitrogen dioxide $NO_2$ |
| nSv | NanoSievert (= $1*10^{-6}$ mSv) |
| PCB | Polychlorinated biphenyls |
| PM10 | Particular air pollution |
| PNET | Primitive neuroectodermal tumours |
| RF | Radio frequency |
| ROC-curve | Receiver operating characteristic curve |
| RR | Relative risk |

| | |
|---|---|
| SCCR | Swiss Childhood Cancer Registry |
| SNC | Swiss National Cohort |
| Sv | Sievert (unit for the equivalent and effective dose) |
| T | Tesla |
| UNSCEAR | United Nations Scientific Committee on the Effects of Atomic Radiation |
| VHF | Very high frequency |
| V/m | Volt per meter (unit for electrical field strength) |
| 95%-CI | 95% confidence interval |

**Definitions**

| | |
|---|---|
| Becquerel | Radioactivity is measured in Becquerel where Becquerel indicates the number of decaying nuclides within a time unit (e.g. within a second) (1, 2) |
| BEIR VII risk model | Dose risk model, developed by the US Committee on the Biological Effects of Ionizing Radiations (3) |
| Down's syndrome | The Down's syndrome is a chromosomal disorder, caused by an excess of the chromosome21, i.e. each cell has three instead of two copies of this chromosome (4). |
| excess risk | also called absolute effect, risk difference or causal risk difference, is the difference in the incidence rates of exposed and unexposed groups in the population (5, 6). Example: the incidence rates for stroke in smokers are 49.6 per 100,000 person-years and in never smokers 17.7 per 100,000 person-years; the excess risk corresponds to the difference between these incidences and equals 31.9 per 100,000 person-years (5) |
| excess lifetime risk | is a measure of excess deaths and corresponds to the lifetime risk from exposure (7) |
| excess relative risk (ERR) | indicates how much the level of risk among exposed is elevated compared to non-exposed people (8). It corre- |

| | |
|---|---|
| | sponds to the relative risk-1. Example: the RR for lung cancer among smokers is 1.36. Thus, the risk for lung cancer among smokers compared to non-smokers is elevated by 36%. |
| liquid tumours | are tumours which occur in the blood, the bone marrow and lymph nodes (9). Such tumours are leukaemia, lymphomas and myelomas (9). |
| N-Nitroso compounds | chemical carcinogens that have been detected in food and drinks (10) |
| solid tumours | are tumours which grow in organ systems (9). Such tumours are for example stomach cancer, lung cancer, liver cancer, thyroid cancer, brain cancer, breast cancer and bladder cancer (11) |
| superoxide dismutase | is an enzyme which helps metabolize oxygen radicals that can cause cells damages |
| UNSCEAR risk model | Dose risk model, developed by the UNSCEAR (3) |

# 1 Introduction and background

## 1.1 Childhood cancer

Childhood cancer is the second most common cause of death after accidents in the developed countries (12, 13). In the developed world childhood leukaemia, central nervous system tumours (CNS tumours) and lymphomas are the most common malignancies in children (14, 15).

Leukaemia results from mutations in haemopoietic stem cells that are located in the red bone marrow (16). It is the most common malignancy for pre-school children (aged 1-4 years) (15). Leukaemia can be broadly differentiated into acute and chronic leukaemias, with the latter being very rare among children (17). Acute leukaemias are further differentiated into lymphoblastic (ALL) and myeloblastic (AML) leukaemia (13). Three quarter of all leukaemia diagnosis are due to ALL which occurs five times more frequently than AML (18). Chronic leukaemias are subdivided into chronic myeloid leukaemias (CML) and chronic lymphoid leukaemia (CLL) (17). Most of the chronic leukaemias are due to CML.

CNS tumours occur almost always in the brain and are classified into astrocytomas, ependymomas, medulloblastomas or primitive neuroectodermal tumours (PNET) and other CNS tumours (19) of which astrocytomas and medulloblastomas or PNET are the most common morphologic groups (19-21). Astrocytomas, ependymomas, medulloblastomas or PNET occur in the brain (22). CNS tumours peak in the age group between 5 and 9 years old (15).

Children are more responsive than adults toward chemotherapy treatments. This fact and the fact that these treatments improved over the last years increased the survival of children diagnosed with cancer, especially with leukaemia (13). For example, it was estimated in a 2007 review that 75-80% of all ALL cases in the United States can be cured (18). Nevertheless, only little is known about the causes for childhood cancers. Environmental risk factors are discussed as possible causes (23).

## 1.2 Environmental risk factors for childhood cancer

In terms of environmental risk factors, children are of special interest since they generally take in greater doses of environmental pollutants by inhaling more air and ingesting more food and water per unit body weight than adults (24). Further, their tissue is more sensitive to ionizing radiation than that of adults (25). Environmental exposures are suspected to be important risk factors for many childhood malignancies. The evidence that environmental risk factors are causal factors for childhood cancer, however, is still limited (14, 17-19, 26, 27). In terms of childhood leukaemia, ionizing radiation is the only established risk factor besides genetic syndromes, such as the Down's syndrome, and chemotherapeutic agents (17). Evidence from ionizing radiation also exists for solid cancers (28-31). Evidence in terms of an association between cancer risk and ionizing radiation is limited to moderate and high dose ionizing radiation, defined as being equal or above 100 miliSievert (mSv) (32). All evidence for an association of moderate and high doses of ionizing radiation with childhood cancer is primarily derived from the Japanese atomic bomb disaster of 1945, elaborated within the Life Span study, and from the more recent Chernobyl disaster in the year 1986.

### *1.2.1 Evidence from moderate and high-dose ionizing radiation: Japanese atomic bomb and Chernobyl disaster*

The Life Span study (29) is considered a high powered study, comprising a large cohort of almost 90,000 Japanese atomic bomb survivors, followed over a long period (from 1950-1990) and reflecting a wide variation of received radiation doses (<5 mSv - >2,000 mSv). The study found the excess risk per unit dose for leukaemia to be three times higher at 1,000 mSv than at 100 mSv. The excess lifetime risk for solid cancers was estimated to be 1.0-1.8 times higher for children, aged below 10 years old, than for persons aged 30 years old at the time of exposure. 50% of the children exposed to the bomb in 1945 died from solid cancers between 1985 and 1990.

Studies on the Chernobyl disaster found strong evidence for an association in children with thyroid cancer but not for leukaemia (33), but evidence has been limited until the recent publication of three cohort studies (28, 30, 31). Unlike the past studies, which

were mostly ecological and case control studies (33), these new Chernobyl studies also considered individual exposure characteristics and potential confounders. The results were found to be consistent between these cohort studies and a strong association with thyroid cancer was confirmed. Tronko et al. (2006) (30), for example, estimated a relative risk of 6.25 (95%-CI: 2.7, 28.5) per Gray (Gy) increase of radioactive iodine for prevalence while Brenner et al.(2011) (28) estimated a relative risk of 2.91 (95%-CI: 1.43, 7.34) per Gy increase of radioactive iodine for incidence of thyroid cancer in children.

### *1.2.2 Other environmental risk factors*

In contrast to medium and high dose ionizing radiation, evidence for an association between childhood cancer and exposure to low doses of ionizing radiation, which is defined as being below 100mSv (32), is limited as investigations on this issue have produced mixed results (34). Evidence for other environmental factors that are also postulated to be associated with childhood cancer is likewise limited (17-19, 26, 27) or has virtually not yet been explored (24). The latter is the case in terms of lead or polychlorinated biphenyls (PCB) exposure and childhood cancers, although epidemiological studies of adults and animal experiments suggested that the exposure could be associated with cancers in humans. With respect to ALL and AML, postulated environmental risk factors - even though with limited evidence - include chemical exposure (solvents (e.g. ethanol), pesticides, hydrocarbons (most importantly benzene)), vehicle exhaust, non-ionizing radiation from electromagnetic fields (EMF), infectious agents, allergens, immunologic isolation, occupational parent exposure, parental smoking, maternal alcohol consumption, diet and age, population density, socioeconomic status and birth order(17). Exposure to EMF, traffic pollution, occupational parental exposure and chemicals (13, 19, 24), along with maternal exposure to N-nitroso compounds during pregnancy and maternal smoking during pregnancy (19) were also postulated to be associated with brain cancer, but the reported associations are inconsistent (19). In terms of chemicals, it remains unclear whether prenatal or postnatal parental exposure is more relevant (24).

### *1.2.3 Study designs and exposure assessment in past epidemiological studies on environmental risk factors*

Many epidemiological studies investigating an association of environmental risk factors with childhood cancer are limited by small case numbers and thus lack statistical power, or have poor exposure assessment and/or study design (17, 19, 24). As childhood cancer is a rare disease (less than 1% of all cancers in developed countries occur in children (20)), past studies on environmental risk factors have most often been case-control studies or ecological studies (17, 24).

Ecological studies are faced with the so-called "ecological fallacy". That is, data in ecological studies are analysed at an aggregated level. Resulting associations cannot be interpreted at the individual level and control for confounding is not possible. According to the Bradford Hill guidelines, which are still regarded as important in assessing whether an association is causal or spurious (35), concluding causation in ecological studies is not possible as other features (i.e. confounders) might be correlated with the environmental factors of interest and at the same time be the real underlying cause for the disease (36).

Case-control studies overcome the limitations of ecological studies as data are analysed at individual level and control for confounding is possible. However, case-control studies are very often faced with recall, participation and selection bias. Recall bias occurs if cases and controls remember inaccurately past exposures or when cases remember past exposure differently from controls (37). The latter results in differential exposure misclassification which might result in either enhanced or attenuated risk estimates if there were a true association. A further bias called selection bias often occurs case-control studies, as not everybody is interested in participating in a study or allows measurements in their home. This bias is of particular concern when it is related to the characteristics of the eligible participants such as their socio-economic status. Past case-control studies on domestic radon exposure and childhood cancer for example that were based on measurements, have reported participation below 55% (38-43). Participation rate among the controls (31%) in one of these studies (38) was much lower than among the cases (50%). Persons with a higher economic status

and better awareness of domestic radon exposure as a public health problem were more interested in participating and thus were more present among the controls than among the cases. However, persons with a higher economic status were found to live in houses with higher measured radon levels than other persons. That in turn probably affected the results, as an inverse-related leukaemia risk was found.

It is very common to use proxies for the assessment of exposure. Examples include use of traffic density, car ownership, gasoline consumption or distance to major roads in terms of atmospheric pollutants (17, 24), and distances to high-voltage power lines (44), proximity to mobile phone stations or broadcast transmitters for electromagnetic fields (19). Exposure proxies simplify the complex exposure distribution. It has also been suggested by Pyatt et al. (2011) (17) that traffic density could correlate with population density which was found to be a risk factor for childhood leukaemia. Although exposure proxies have been shown to be useful, they might introduce uncertainties and bias in the corresponding studies.

Hence, despite limited evidence, many possible risk factors cannot be ruled out to be associated with childhood cancer. Due to the established evidence for an association between high dose ionizing radiation and childhood cancer, given that evidence from low-dose ionizing radiation is less clear and as the tissue of children is more sensitive to ionizing radiation than that from adults, research on low-dose ionizing radiation and childhood cancer was considered to be the major topic of this thesis.

## 1.3 Ionizing radiation

Ionizing radiation, also referred to as radioactivity, results from the decay of radioactive nuclides (2, 45). Radioactivity is measured in Becquerel (1). Most of the ionizing radiation results from natural sources (2, 46). It was estimated that less than 10% of the received radiation by humans would be anthropogenic (47). Before the end of the nineteenth century, ionizing radiation from natural sources was the only source by which humankind was affected. This changed with the discovery of x-ray radiation by Wilhelm Röntgen and of radioactivity by Henri Becquerel in the 1890s (2). Besides ionizing radiation from medical exposure (e.g. x-ray irradiation), anthropogenic modified

ionizing radiation stems from fall-outs from atomic bombs, nuclear accidents and nuclear tests (48).

Ionizing radiation can be classified into alpha (α)-, beta (β)-, gamma (γ)- and x-ray radiation (2, 45). Alpha radiation consists of alpha-particles which are helium nuclei, resulting, for example, from the decay of Uranium, radon or Plutonium (48). It is characterized by low penetration depth due to the high energy loss per unit distance travelled (2, 49), thus alpha particles might be stopped in the outer layers of the skin (49) (Figure 1). Beta radiation consists of beta-particles which are electrons. Beta particles have a higher penetration depth than alpha particles, able to penetrate up to 2cm of a living tissue (2) (Figure 1). Beta radiation results from the decay of potassium (K), Strontium (Sr) or Caesium (Cs) ,for instance (48). Gamma radiation consists of photons, has a very high penetration depth that is able to traverse the human body (2, 49) (Figure 1). X-rays are used for diagnostic procedures and in order to be useful, they must penetrate the human body (2).

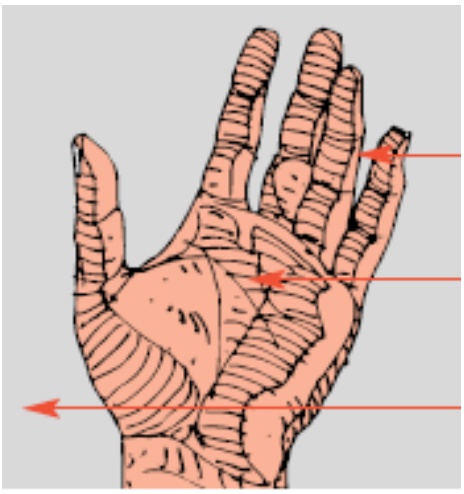


**Figure 1: Penetration depth of alpha, beta and gamma rays taken at the example of the hand. While alpha particles are stopped at the outer layer of the skin of the hand and beta rays are stopped within the tissue of the hand, gamma rays traverse the hand (Source: Federal Office of Public Health, (2007) (50))**

As mentioned above, a further differentiation is typically made between high dose ionizing radiation and low dose ionizing radiation, with the latter defined as below 100mSv (32).

Ionizing radiation removes electrons from atoms and molecules in the human body (2, 48, 51). This involves the induction of chemical changes that in turn influence the functioning of organs and cells (2, 48). It has been shown in leukemic-cells from leukaemia patients, for example, that ionizing radiation leads to chromosomal translocations, deletion of chromosomal segments or of individual genes and duplication of chromosomes that in turn can lead to malignant transformations (33, 52). These chromosomal rearrangements are due to DNA damage that is caused by ionizing radiation (33). It has also been shown by *in vitro* experiments that the exposure of cells to ionizing radiation leads to a reduction of superoxide dismutase activity, i.e. oxygen radicals cannot be metabolized, that can cause cell damages (25). It was further found that apoptosis, i.e. a mechanism which involves the elimination of damaged cells and thus an important mechanism in the prevention of cancer, is probably not effective at very high doses of ionizing radiation (25). In terms of radon, it has also been speculated that radon gas might damage stem cells which in turn results in the development of leukaemia (52). This, however, has rarely been investigated and knowledge about the effects of radon on stem cells remains limited (53).

## 1.4 Radioactivity in the environment

Low-dose ionizing radiation from natural sources may be atmospheric (i.e. cosmic) or terrestrial in origin (2). Extraterrestrial radiation stems from cosmic rays in the atmosphere (2). Cosmic rays interact with the nuclei of the earth's atmosphere and result in radiation consisting of neutrons, electrons, gamma and X-rays and in the production of radionuclides (tritium ($^{3}H$), radiocarbon ($^{14}C$)) that can be found in food and drinks (54, 55). The intensity of this radiation decreases with decreasing altitude above sea level (55). Due to the shielding of buildings, doses from cosmic rays are estimated to be reduced by 20% indoors (56). Terrestrial radiation originates either from gamma rays from radionuclides in rocks and soils or radon and its decay products in the air. Such radionuclides in rocks and soils are Uranium-238 and thorium-232 but also potassium-40 (55). These radionuclides can also be found in building materials. Building materials are regarded as contributing significantly to the doses from natural gamma rays (56). However doses vary, depending on the amount of such radionuclides in

building materials. Doses also vary depending on the ground beneath buildings and the degree of shielding provided by the building material (56). Due to their higher Uranium content, terrestrial radiation is higher in regions with crystalline (i.e. granitic and metamorphic) rocks but lower in regions with sedimentary rocks such as limestone (55). It is also higher in buildings, build of granitic and metamorphic stones.

Radon finally is a radioactive gas and a nuclide of a long radioactive decay chain, originating from Uranium-238 (57-59) where its decay products emit alpha particles (60). Radon mostly emanates from rocks and soils into the atmosphere and through cracks and holes in the building fundament into dwellings (Figure 2) (61, 62). Radon however might also be found in drinking water or emanate from building materials, the latter depending on the Uranium content of the building stones (8). Radon is able to travel a long distance before it decays (62). It is diluted outdoors (1) but is able to accumulate inside of buildings which is due to lower air pressure inside buildings (63). Depending on geology, soil permeability but also on different building characteristics which correlate with building permeability (housing type, year of construction, type of fundament, sealing between houses and the ground) and air exchange rate (daily room ventilation, type of fundament) (8), there is however a wide variation between different buildings.

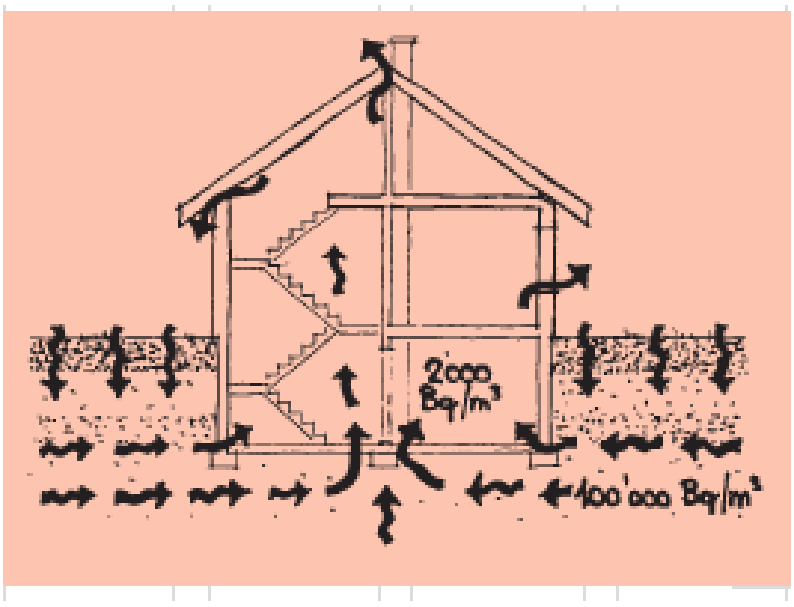


**Figure 2: Emanation of radon from soils into buildings. (Source: Federal Office of Public Health, (2000) (1))**

## 1.5 Doses to humans

In terms of doses to humans, there is a distinction between irradiation derived from external versus internal ionizing radiation. Due to their strong penetration depth, gamma rays from radionuclides in rocks and soils and cosmic radiation are mainly responsible for external irradiation (2). Doses from both, cosmic rays and terrestrial gamma rays are uniform across the body (64). Alpha particles are mainly responsible for internal radiation since they have a low penetration depth and are stopped at the outer layer of the skin (2). Internal alpha radiation occurs via the inhalation of radon gas or its decay products. But internal irradiation also occurs through the ingestion of radioactive nuclides (e.g. potassium, tritium, radiocarbon) in food and drinks. When ingested or inhaled, the physical half-life of the isotope, biological processes and metabolism might affect the distribution of the received dose. Thus, doses from alpha-particles are not homogenously distributed between tissues (64).

When considering doses to the human body, one has to differ between absorbed, equivalent and effective doses (Figure 3).

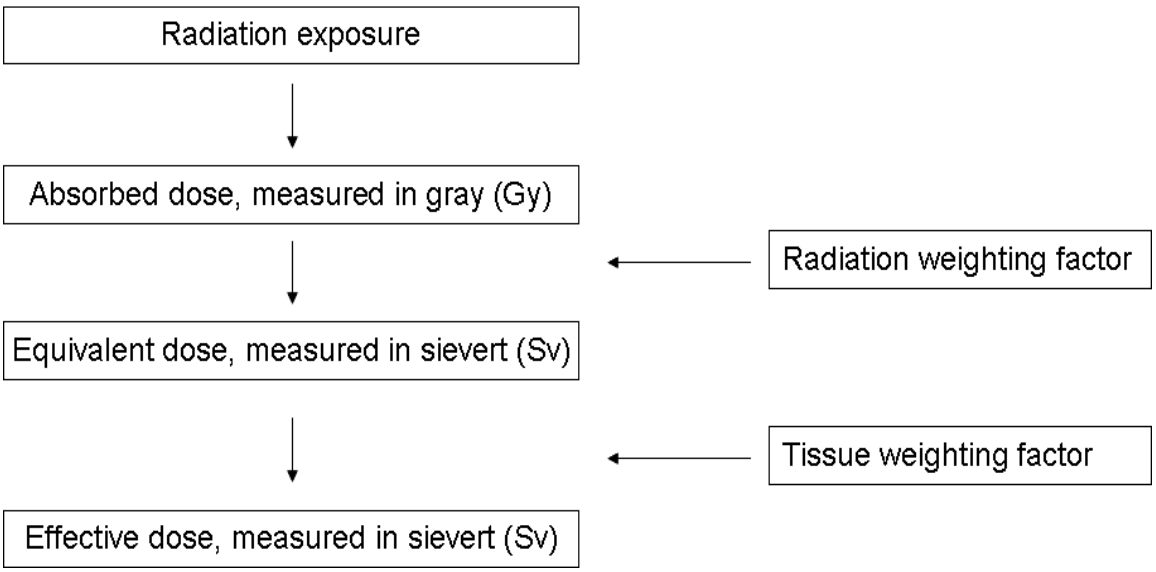


**Figure 3: Absorbed, equivalent and effective dose, based on Harrison et al. (16).**

An absorbed dose is the energy, caused by ionizing radiation, which is actually absorbed by an organ or tissue (2). Its unit is given in gray (Gy) (2). In general, the ab-

sorbed dose for gamma radiation is estimated to be a factor of 30 larger than that from alpha radiation (46).

When dose estimations to particular organs are presented in the literature, they are often referred to the equivalent organ doses (46, 60, 65). This is a measure for the biological effectiveness (i.e. chromosomal aberration, neoplastic transformations (49)) of the ionizing radiation on a body organ or a tissue (2). It corresponds to the absorbed dose, multiplied by a weighting factor that depends on the different types ionizing radiation (i.e. alpha, beta, gamma) (16). This weighting factor reflects the degree of relevant biological damage of the different ionizing radiation types (64). The weighting factor is higher for alpha radiation than for gamma radiation and cosmic rays, with the exception of neutrons (46). It corresponds to 20 for alpha particles and 1 for gamma radiation (46), which implies that the biological effectiveness of an absorbed dose of 0.1 Gy of alpha particles is the same as an absorbed dose of 2 Gy of gamma particles (49). As shown in Figure 1, the unit of the equivalent dose is given in Sievert (Sv) (16).
However, it is important to note that gamma radiation has a higher penetration depth than alpha radiation. This might explain the higher equivalent doses from terrestrial gamma radiation and cosmic radiation compared to equivalent radon doses for tissues such as red bone marrow (Table 1).

**Table 1: Annual equivalent doses (mSv) for red bone marrow from terrestrial gamma rays, cosmic rays and domestic radon exposure, based on estimates for the UK (60, 66)**

| | 1 year old | 10 years old | adult |
|---|---|---|---|
| Radon-222[1] | 0.08 | 0.08 | 0.08 |
| Terrestrial gamma rays[2] | 0.42 | 0.38 | 0.33 |
| cosmic rays[2] | 0.39 | 0.35 | 0.31 |

[1] values refer to a radon level of 20 Bq/m³ and to absorbed doses of 5.0 µGy/year for a one year old child, of 4.8 µGy/year for a 10 year old child and to absorbed doses of 4.6 µGy/year for a 15 year old child

[2] values refer to absorbed doses of 810 µGy/year for a one year old child, of 830 µGy/year for a 10 year old child and to absorbed doses of 640 µGy/year for an adult

The effective dose (Figure 1) further considers varying sensitivities of different organs and tissues to ionizing radiation (2). This sensitivity is higher for organs such as the lung or the red bone marrow than for organs such as the skin or the brain (Table 2). Given for example that gamma radiation is uniformly distributed across the body, it is expected that gamma radiation plays a more important role in terms of leukaemia than in terms of other tumours (such as brain tumours) as the red bone marrow is more sensitive to ionizing radiation. The effective dose is used to indicate the overall health from ionizing radiation and corresponds to the sum of the products of the equivalent organ doses multiplied with a tissue weighting factor (16). The unit of the effective dose is also given in sievert (Sv). Considering the different sources of natural radiation worldwide, about half of the annual effective dose (1.3 mSv) to humans is due to radon exposure and one half (1.1 mSv) from radiation from cosmic rays, terrestrial radiation and the ingestion of radionuclides in food and drinks (Figure 4) (2).

**Table 2: Tissue weighting factors (67)**

| Tissue | Tissue weighting factor (wt) |
|---|---|
| bone marrow (red), colon, lung, stomach, breast | 0.12 |
| gonads | 0.08 |
| bladder, oesophagus, liver, thyroid | 0.04 |
| bone surface, brain, salivary glands, skin | 0.01 |

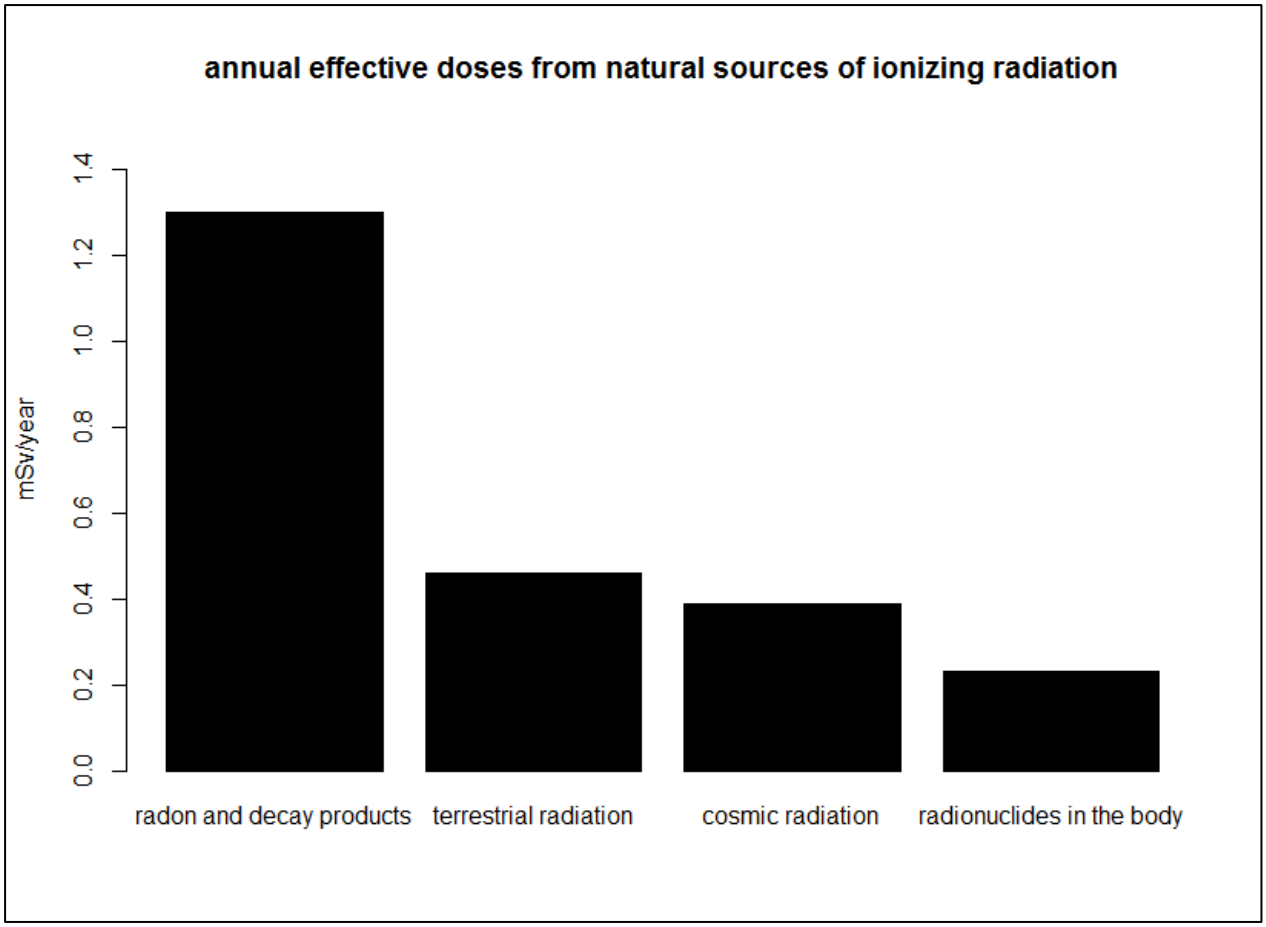


**Figure 4: Worldwide average annual effective dose from natural sources (2)**

## 1.6 Ionizing radiation from natural sources and childhood cancer - state of the research

Due to its influence on the functioning of organs and cells, ionizing radiation is thought to be an important environmental factor in terms of cancers in children. Low-dose ionizing radiation from natural sources, which is often denoted as natural background radiation in the literature is ubiquitous. While harmful effects of high-dose ionizing radiation have been well documented, much less is known about the relationship between low-dose radiation and cancer. Recently, the percentage of leukaemia cases, attributable to natural background radiation was estimated to be between 15% (using BEIR VII risk model) and 20% (using UNSCEAR risk model) (3). These estimations were based on dose estimations to the red bone marrow, leukaemia mortality data from atomic bomb survivors and considered factors such as gender, age at exposure and time since exposure. Based on these results, it was assumed that low dose ionizing radiation might be likewise a risk factor for childhood leukaemia (3). However, only few epidemiological studies are available on this issue and little evidence for an effect from low-dose ionizing radiation is available.

Concerning gamma radiation, two ecological study on natural gamma radiation were published (68, 69), one of them (68) reported no association with childhood leukaemia (68) while the other one (69) reported a negative association between gamma radiation and childhood leukaemia. The same inconsistency applies to case-control studies. While a smaller Swedish study (70) reported an association between natural gamma radiation and childhood leukaemia, a larger British case-control did not find such an association between natural gamma radiation and childhood leukaemia (71). However, a non-significant dose response trend for CNS tumours was visible in the latter study. Nevertheless, participation of eligible study participants in the British study was low, as measurements for only 49% of the 3,838 eligible cases and for 43% of the 7,629 eligible controls were carried out. Given an exposure, ranging from an absorbed dose of below 0.1 mGy/year to 2.03 mGy/year, the British study was considered to be underpowered to detect a possible association with childhood leukaemia (72) and with the exception of socio-economic status, no other potential confounders were consid-

ered. The Swedish study adjusted for age only and did not consider other potential confounders either. Recently, a large record-based case-control study from the United Kingdom, published in 2012, reported an elevated, significant risk for leukaemia with increasing dose of natural gamma radiation (73). Risks for other cancers such as CNS tumour were less elevated and did not reach statistical significance.

Past studies on domestic radon exposure have also not found compelling evidence for an association with childhood cancer. This is in contrast for lung cancer in adults, where the risk has been established by studies on underground miners (63) and on domestic radon exposure (74, 75). A recent review summarized results from past ecological and case-control studies on domestic radon exposure and childhood leukaemia (52). The results of the studies listed in these reviews have been inconsistent whereas several of them reported an association between domestic radon exposure and childhood cancer. According to Hill, consistency of the observed association, i.e. that it has been repeatedly observed considering different approaches, is an important criterion to be fulfilled in order to assess an association as causal and not as spurious (36). Hence, like an earlier review (76), the authors of this recently published review (52) found insufficient evidence to confirm that domestic radon exposure is associated with childhood leukaemia. Further, the focus of these studies was mostly on childhood leukaemia with only few studies investigating the association with central nervous system tumours (CNS tumours).

In the review for this thesis, 8 case-control studies (38-43, 73, 77) and 13 studies with an ecological design (78-90) were identified. Although the majority of the ecological studies reported an elevated childhood leukaemia risk, evidence from these studies is limited. Exposure assessment on an aggregated level becomes even more problematic, as radon concentrations might differ between neighbouring homes due to their different building characteristics. In Switzerland, building characteristics such as building age and building type where identified as important predictors for domestic radon concentrations (91) where higher radon levels were predicted for detached houses than for apartments or for older buildings than newer ones (92).

## 1.7 Non-ionizing radiation

Non-ionizing radiation comprises radiation from electromagnetic fields (EMF) and optical radiation (infrared, visible and ultraviolet light) (Figure 5). As with ionizing radiation, non-ionizing radiation is part of the electromagnetic spectrum and is characterised by its wavelength, expressed in meter and its frequency, expressed in Hertz (Hz) (Figure 5). In contrast to ionizing radiation, non-ionizing radiation has insufficient energy to ionize atoms and molecules and thus to damage the DNA (93, 94). This is due to the lower frequency and the longer wavelength of non-ionizing radiation.

Non-ionizing radiation from electromagnetic fields (EMF) is subdivided into extremely low-frequency electromagnetic fields (ELF-EMF) (> 0-100 kHz) and radiofrequency electromagnetic fields (RF-EMF) (100 kHz – 300 GHz) (94). Static fields (0 Hz) were recently also considered to belong to electromagnetic fields (95).

ELF-EMF are produced from high voltage power lines or electrical installations. In terms of ELF-EMF, it is possible to distinguish between electric and magnetic fields. Electric fields are created by electric charges and measured in volts per metre (V/m) (44) that corresponds to the electric field strength. The magnitude of the electric current determines magnetic fields that are measured in Tesla (T) (44). ELF-EMF induce electric fields and current in tissues (96).

RF-EMF are produced from radio- and TV transmitters, mobile phone base stations and mobile phones, and are responsible for heating of cells and tissues when absorbed (97). In terms of RF-EMF exposure, there is a distinction between near-field exposure and far-field exposure. Near-field exposure sources such as mobile and cordless phones are applied close to the body, that is mainly to the head where they cause high and periodic short-term exposure (98). Far-field exposure sources such as broadcast transmitters and mobile phone base stations on the other hand cause lower but continuous, uniform exposure across the whole body (98). Far field exposures also differ by source. Broadcast transmitters are spaced far apart, located at few sites only but, individually, cover large areas and therefore generate relatively high fields at ground level (97). Mobile phone base stations on the other hand cover smaller areas, generate

lower fields than broadcast transmitters (99) but are more common than radio and TV transmitters. A recent study, examining the importance of different RF-EMF sources, estimated that mobile phone base stations accounted for 32% of the total RF-EMF exposure between 2007 and 2008 whereas the corresponding figure for broadcast transmitters was 11.7% for the same time period (98). However, exposure to RF-EMF was dominated by broadcast transmitters prior to the introduction of mobile and cordless phones in the 1990s (98).

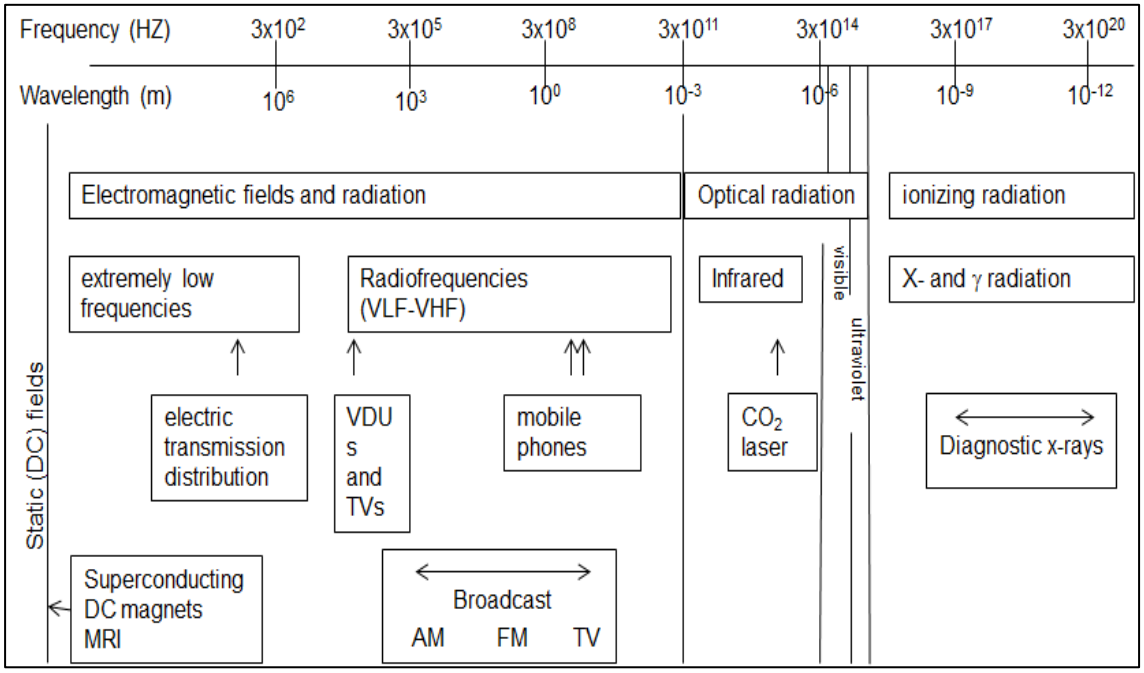


**Figure 5: Electromagnetic spectrum, based on Kheifets et al. (2005) (99) and IARC (2002) (93). AM: amplitude modulation, DC: direct current, FM: frequency modulation, MRI: magnetic resonance imaging, TV: television, VDU: visual display unit, VHF: very high frequency, VLF: very low frequency**

The increase of EMF-exposure in the recent decades has raised concern on a possible association with childhood cancer but corresponding research is still controversial. The IARC (International Agency for Research on Cancer) evaluated extremely low-frequency magnetic fields (ELF-MF) as possibly carcinogenic, based studies on childhood leukaemia (93). Consistent epidemiological results were reported from published pooled analyses on exposure to ELF-MF and childhood leukaemia. These pooled analyses suggested an association between ELF-MF and childhood leukaemia (100-102). Biological mechanism which could explain such an association are the re-

duction of melatonin levels due to EMF exposure or cell proliferation due to the induction of electrical fields (94). However, animal and in-vivo and in-vitro studies on ELF-EMF exposure and cancer so far produced inconsistent results (93) and evidence in terms of this health outcome in relation to ELF-EMF exposure can still be regarded as being limited.

Radiation from near-field RF-EMF exposure has raised concern in terms of brain tumours due to the application of mobile phones close to the head. Penetration of radio-frequency relative to the head size is greater for children than for adults (44). It is further assumed that children would be more sensitive to RF-EMF due to their developing nervous system, the higher water content and higher ion concentration in their brain tissue (99). The latter factors result in a more conductive brain tissue for children than for adults (99). Despite the heating of cells and tissues from RF-EMF exposure when absorbed, in vitro, in vivo and animal studies have not found evidence for genotoxic effects, i.e. for effects, causing DNA- and chromosomal damage from RF-EMF exposure (97, 103). However, the IARC (104) classified RF-EMF as possible carcinogenic, based on reported positive associations between central nervous system and brain tumours and exposure to RF-EMF from wireless phones among adults (105, 106).

In terms of exposure to RF-EMF and childhood cancer, few studies are available. Most of the studies are on far-field RF-EMF exposure, related to broadcast transmitters, with an ecological- (107-113) or a case-control study design (114-116). Very few studies on near-field RF-EMF exposure and childhood cancer have been published. We identified only two case-control studies on mobile phone base stations and childhood cancer (117, 118) A recent review did not find studies on mobile phone exposure and childhood leukaemia (95). With the exception of a recently published case-control study (119) which did not report a causal association between mobile phone use and brain tumours in children, no other studies in children are available.

Exposure assessment in studies on broadcast transmitters and childhood cancer was mainly based on proximity to the nearest transmitter station (107-110, 112-115). A recent letter criticized distance-based approaches, indicating that such approaches would be a good proxy for each single transmitter but not for all transmitters com-

bined (120). An approach of using distance to the transmitter station as proxy for RF-EMF exposure is especially problematic for areas where the fields of different broadcast transmitters overlap. In such situations, a better approach would be to consider cumulative RF-EMF exposure to different broadcast transmitters. Second, factors such as the local topography or the vegetation add to the complexity of the exposure distribution of RF-EMF from radio and TV transmitters due to shielding, diffraction or the reflection of RF-EMF (121). Such factors cannot be considered when using distances to the nearest transmitter station as proxy for RF-EMF exposure from broadcast transmitters. As data on modelled field strengths from broadcast transmitters were available, research on RF-EMF exposure from broadcast transmitters and childhood cancer was considered to be another topic of this thesis.

# 2 Framework and aims of this thesis

## 2.1 Ionizing and non-ionizing radiation and the risk of childhood cancer

Radon is the major source of low-dose ionizing radiation exposure for humans. The main issue of this dissertation was therefore to assess whether domestic radon exposure is associated with childhood cancers. An objective was to develop an exposure model to predict radon concentrations for all Swiss households and each individual for this assessment. A second objective consisted in evaluating this exposure model by comparing it with another exposure assessment method. Based on the radon prediction model, we assessed whether domestic radon exposure is associated with childhood cancer. In view of the conflicting results of past studies, a second aim was to assess whether low-dose ionizing background gamma radiation is associated with childhood cancers. A further section is dedicated to non-ionizing radiation from far-field RF-EMF sources, where it was the aim to assess whether RF-EMF from radio and TV transmitters is associated with childhood cancers.

Prospective census-based cohort designs were performed to assess the three subject areas, considered within this dissertation. All children, aged less than 16 years and living in Switzerland at the date of census 2000 (December 5$^{th}$ 2000) were considered for the analyses. Time at risk was set to begin at census and lasted until the date of diagnosis, death, or emigration, the child's 16th birthday or December 31st, 2008, whichever occurred first. Children were excluded from the cohort if their exact place of residence was unclear. We used data from the Swiss National Cohort (SNC) which is a longitudinal research platform, based on the linkage of census data from 1990 and 2000 and containing data from all buildings, households and persons at the time of census. Incident cancer cases in the SNC were identified by means of a probabilistic linkage with the Swiss Childhood Cancer Registry (SCCR) using information on date of birth, gender, place of residence, place of birth and parent's dates of birth if available. Separate analyses were carried out for childhood leukaemia and central nervous system tumours (CNS tumours). With respect to leukaemia, ALL was explored separately

given that they do not have the same risk factors. This further allows for the possibility to detect potential aetiological relationships within the leukaemia subclasses (17).

## 2.2 Aims of this thesis

**Aim 1: to assess whether domestic radon exposure is associated with childhood cancer**

***Objective 1:*** to develop a radon prediction model to estimate concentrations at households in Switzerland

The exposure model which we developed was a log-linear regression model. It was developed and validated on the basis of a large database with measurements for various rooms of almost 7% all Swiss buildings, carried out all over Switzerland and collected homogenously by the Federal Office of Public Health (FOPH). The model was based on 44,631 measurements collected between 1994 and 2004. Of these, 80% randomly selected measurements were used for model development and the remaining 20% for an independent model validation. Identification of relevant predictors was based on evidence from the literature, the adjusted $R^2$, the Akaike's information criterion (AIC) and the Bayesian information criterion (BIC). The prediction model was evaluated by calculating Spearman rank correlation between measured and predicted values. To assess exposure misclassification, the sensitivity, specificity, the weighted Kappa statistic and area under the receiver operating characteristic (ROC) curve, i.e. a graph of sensitivity vs. 1-specificity, were calculated. The prediction model as well as its evaluation are broadly discussed in Article 1.

***Objective 2:*** to evaluate the radon prediction model for exposure assessment, through comparison with a measurement-based exposure assessment

A main issue in past environmental epidemiological studies is inadequate exposure assessment. This also applies to radon exposure assessments where measurement sites have often been selected in a non-representative way. Different approaches are possible to overcome the problem of non-representative selection of measurement sites. One possible approach is a model-based approach where radon concentrations

for all households and persons on individual level are estimated. An example is our study on domestic radon exposure and the risk of childhood cancer where exposure assessment was based on the radon prediction model, described in Article 1. However, other approaches are likewise possible. Recently, measurement-based predictions were published within a health impact assessment, determining the number of lung cancer deaths attributable to residential radon (122). The authors of this study considered the population distribution within municipalities and within buildings for their exposure assessment. They employed measurements from the FOPH radon database (while excluding measurements from households, situated in basements). They aggregated mean measured radon levels to municipality level by incorporating the average floor distribution and population weighting. Based on these calculations, radon levels for each canton and for Switzerland were estimated. We compared these two approaches and assessed their advantages but also their limitations in terms of radon exposure assessment. These two approaches are broadly discussed in Article 2.

***Objective 3:*** domestic radon exposure and the risk of childhood cancer

For this objective about domestic radon exposure and the risk of childhood cancer, indoor radon exposure was assessed at baseline (date of census 2000) for each child's home address. The data were analysed using Cox regression models with age as the underlying time scale. The models were adjusted for gender, birth order within each household, socio-economic status of the parents, background gamma radiation exposure (cosmic, terrestrial, and artificial ground radiation from the Chernobyl event) and period effects. Full descriptions as well as the results of these analyses are presented in Article 3.

**Aim 2:** to assess whether exposure to background gamma radiation is associated with childhood cancer

For this objective about background gamma radiation and childhood cancer, exposure assessment was based on dose rates from outdoor gamma radiation. Dose rates from cosmic and terrestrial radiation were available from the Swiss radiation map (123) with a grid cell resolution of 2km. Doses rates from artificial ground radiation from the

Chernobyl fallout (Southern part of Switzerland, 1986) were also available from the Swiss radiation map. Gamma dose rates from these three different sources were considered for the analyses. The radiation map was derived from models and from measurements. Dose rates from cosmic radiation were estimated from a digital height model, based on the Swiss National Map 1:25,000 (124). Doses rates from artificial and terrestrial radiation were based on airborne spectrometry measurements, and in the case of the latter also on gamma-ray spectrometry measurements and rock/soil sample data. Exposure to outdoor background radiation was assessed at baseline (date of census 2000) for each child's home address. The same was done for exposure to indoor radon concentrations using the radon prediction model, described in Article 1.

The data were analysed using Cox regression models, dividing the children in three exposure groups with cut-off points at the 50$^{th}$ and 90$^{th}$ percentile. To elaborate the exposure-response association, a linear exposure-response analysis was also conducted using gamma dose rates as continuous predictor. Hazard ratios were expressed per 100 nSv/h increase. The regression models were adjusted for age, gender, birth order within each household, domestic radon exposure, socio-economic status of the parents and period effects. Tests for the same potential confounding factors as for the analyses on domestic radon exposure and childhood cancer, described in Article 3, were carried out. None of them proved to be a confounder and were omitted from all models. Subgroup analyses, stratified by age are also presented, given that young children may be more vulnerable to exposure from ionising radiation than older children (72). Another subgroup analysis considered the effect of residential mobility. The SNC contains information on living place five years prior to the census. For children aged 5-15 years, it was known if they had moved within the five years prior to the census. Thus, separate analyses are provided for children who did not move and those who moved between 1995 and 2000.

For the analyses on background gamma radiation, no publication has been planned so far. Instead, the results are presented in chapter 4 of this dissertation. They are further summarized in chapter 6 and discussed in chapter 7 of this dissertation.

**Aim 3:** to assess whether exposure to radiofrequency electromagnetic fields from broadcast transmitters is associated with childhood cancer

For this aim about the cancer effects of non-ionizing radiation from broadcast transmitters, two types of analyses were conducted. First, a time to event analysis similar to the analyses on domestic radon exposure and the analyses on background gamma radiation and childhood cancer was carried out, applying Cox regression models. The models were adjusted for age, gender, background gamma radiation, benzene exposure and distance to the next high voltage power line. Second, a Poisson regression analysis was conducted, considering all children, aged less than 16 years and living in Switzerland between 1985 until 2008. For the Poisson regression analysis, person years were aggregated by exposure categories for calendar year, gender, one year age strata and estimated by inter-/extrapolation from the census years 1990 and 2000.

For the exposure assessment of the study participants, field strengths from short-wave and medium-wave radio transmitters, from analogous TV-transmitters, digital Radio and digital TV transmitters were modelled by the Federal Office of Communications. The antenna height, the transmission duration, direction of the emissions and the local topography were considered for the field strength calculations. For the time-to-event analysis, exposure was assessed again at baseline (date of census 2000) for each child's home address. For the Poisson regression analysis, place of residency at the time of diagnosis was used for the exposure assignment. A full description as well as the results of these analyses is presented in Article 4.

# 3 Domestic radon exposure and the risk of childhood cancer

## Article 1: A prediction model for assessing residential radon concentration in Switzerland

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# A prediction model for assessing residential radon concentration in Switzerland

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ABSTRACT

Indoor radon is regularly measured in Switzerland. However, a nationwide model to predict residential radon levels has not been developed. The aim of this study was to develop a prediction model to assess indoor radon concentrations in Switzerland.

The model was based on 44,631 measurements from the nationwide Swiss radon database collected between 1994 and 2004. Of these, 80% randomly selected measurements were used for model development and the remaining 20% for an independent model validation. A multivariable log-linear regression model was fitted and relevant predictors selected according to evidence from the literature, the adjusted $R^2$, the Akaike's information criterion (AIC), and the Bayesian information criterion (BIC).

The prediction model was evaluated by calculating Spearman rank correlation between measured and predicted values. Additionally, the predicted values were categorised into three categories (50th, 50th–90th and 90th percentile) and compared with measured categories using a weighted Kappa statistic.

The most relevant predictors for indoor radon levels were tectonic units and year of construction of the building, followed by soil texture, degree of urbanisation, floor of the building where the measurement was taken and housing type ($P$-values $<0.001$ for all).

Mean predicted radon values (geometric mean) were 66 Bq/m$^3$ (interquartile range 40–111 Bq/m$^3$) in the lowest exposure category, 126 Bq/m$^3$ (69–215 Bq/m$^3$) in the medium category, and 219 Bq/m$^3$ (108–427 Bq/m$^3$) in the highest category. Spearman correlation between predictions and measurements was 0.45 (95%-CI: 0.44; 0.46) for the development dataset and 0.44 (95%-CI: 0.42; 0.46) for the validation dataset. Kappa coefficients were 0.31 for the development and 0.30 for the validation dataset, respectively. The model explained 20% overall variability (adjusted $R^2$).

In conclusion, this residential radon prediction model, based on a large number of measurements, was demonstrated to be robust through validation with an independent dataset. The model is appropriate for predicting radon level exposure of the Swiss population in epidemiological research. Nevertheless, some exposure misclassification and regression to the mean is unavoidable and should be taken into account in future applications of the model.



## 1. Introduction

There is evidence that radon exposure increases the risk of lung cancer in adults (Krewski et al., 2006). However, less is known with respect to the association with childhood cancer, in particular to childhood leukaemia, the most common type of childhood cancer (Miller et al., 1994). Previous case-control studies have reported inconsistent results (Cartwright et al., 2002; Kaletsch et al., 1999; Lubin et al., 1998; Maged et al., 2000; Raaschou-Nielsen et al., 2008; Steinbuch et al., 1999; Stjernfeldt et al., 1987), whereas ecological studies have found an association between childhood leukaemia and indoor radon concentration (Collman et al., 1991; Evrard et al., 2005, 2006; Henshaw et al., 1990; Kohli et al., 2000; Lucie, 1989; Muirhead et al., 1991; Richardson et al., 1995; Thorne et al., 1996). Despite this, evidence from ecological studies is limited because confounding can not be controlled.

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Although Switzerland is a relatively small country, it comprises a wide variation in geology and soil types. Radon is a nuclide of a long radioactive decay chain originating from uranium, a naturally occurring element in granitic and metamorphic rocks (Ball et al., 1991; Gillmore et al., 2005; Gunderson, 1992). Soil texture and the occurrence of subsoil horizons determine the gas and water permeability of soil, thereby influencing the radon gas flow to the surface (Nazaroff, 1992; Nero and Nazaroff, 1984; Tanner, 1980). Geologic faults, elevation above sea level and degree of incline also serve as indicators of soil permeability (Mose et al., 2010; Varley and Flowers, 1993). Building characteristics such as housing type and year of construction are considered relevant for prediction of indoor radon levels as they can be correlated with building permeability (Andersen et al., 2007; Gerken et al., 2000; Gunby et al., 1993; Hunter et al., 2009; Verdi et al., 2004). The floor/storey within a building (ie. ground floor, first floor, etc.) is a relevant factor for radon exposure, as radon gas concentrations are known to be lower in upper floors due to the greater distance from the soil and rocks beneath the building (Gerken et al., 2000; Gunby et al., 1993; Papaefthymiou et al., 2003; Sundal et al., 2004). Room ventilation attenuates radon levels, and room type has been used as a proxy for ventilation in several studies (Clouvas et al., 2007; Venoso et al., 2009).

Although indoor radon concentrations have been regularly measured since 1981, radon exposure has not been previously modelled in Switzerland. Radon measurements are routinely collected by the Federal Office of Public Health (FOPH) and stored in a comprehensive radon database. Currently, the database includes173,548 measurements covering almost 7% buildings in Switzerland. Measured indoor radon concentrations vary widely: floor and population-corrected estimated arithmetic mean indoor radon concentrations of occupied buildings per canton range from 29 Bq/m$^3$ in the canton of Geneva to 147 Bq/m$^3$ in the canton of Ticino (Menzler et al., 2008).

A radon exposure model based on available measurements would allow assessment of radon exposure at many more sites than would be possible with measurements alone, given the large number of study participants that would be required. In addition, performing measurements may introduce participation bias. Measurements may even be misleading if exposure levels back in time are to be assessed.

The aim of this paper was to develop and validate an empirical regression model to allow the prediction of indoor radon concentrations for inhabited rooms in all Swiss dwellings, using the Swiss radon database in combination with a large number of predictor variables for all regions and buildings in Switzerland.

## 2. Material and methods

### 2.1. Radon data

The study employed 44,631 radon measurements form the FOPH database, collected between 1994 and 2004. From the total 87,787 measurements in the database collected between 1994 and 2004, 35,823 carried out in basements or uninhabited rooms were excluded, given the study's aim of predicting indoor radon concentrations for inhabited rooms (defined as heated rooms). Measurements were also excluded due to inaccurate coordinates (6,908 measurements) or for other reasons (see Fig. 1). Coordinates were judged to be incorrect if they referred to the centre of a municipality or if the municipality name in the database did not match with the coordinates.

Of the 44,631 remaining measurements, 80% from each canton were randomly selected for the model development dataset, and the remaining 20% from each canton were used for model validation.

### 2.2. Radon database

The radon database captures site-specific information including housing type, year of construction, floor of the building, and type of room. Measurement-related information is also recorded, including type of dosimeter, the measurement period (start date and end date), and the municipality where the measurements took place.

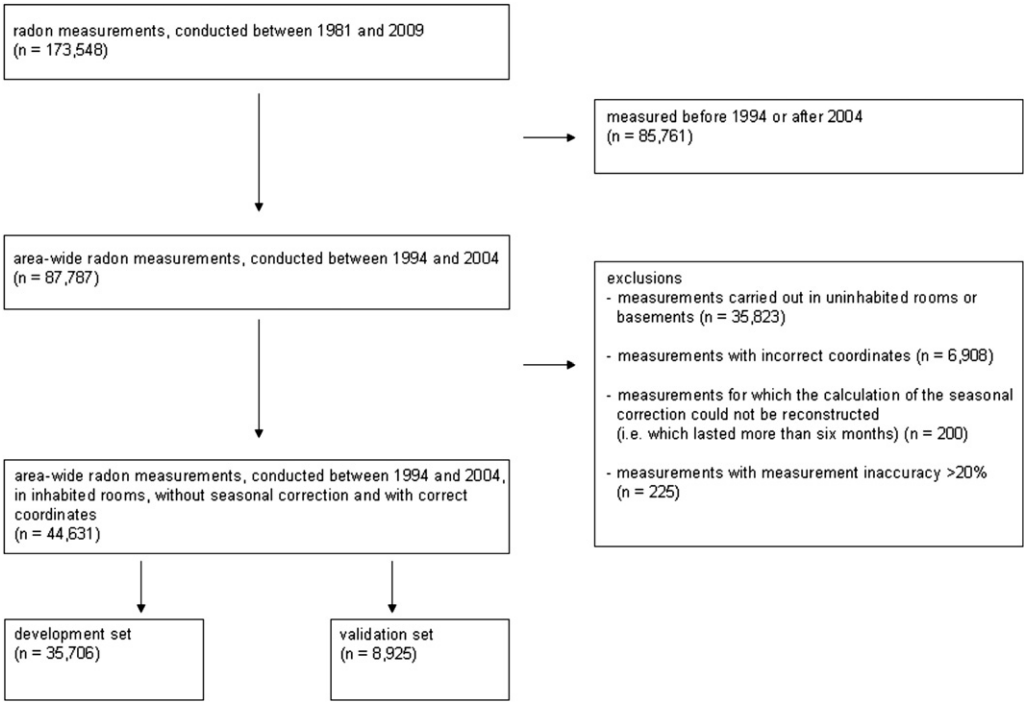


**Fig. 1.** Selection procedure of the measurement, considered for model development and validation.

### 2.3. Building registry

The future nationwide application of the prediction model would need to be based on the national building registry. Consequently, only variables included in the building registry were included in the prediction model. The building registry contains data for all buildings and households in Switzerland, including year of building construction, inhabitants as determined by the national census of 2000, and the floors occupied by these households. As data relating to the type of building were coded differently to that in the radon database, a comparable housing type variable was reconstructed based on the number of floors in the building, the number of housing units/flats and whether the buildings were residential or used for other purposes, including farming houses.

Two recent publications recommend considering schools when applying housing type as predictor due to different air exchange rate between homes and schools (Clouvas et al., 2007; Venoso et al., 2009). An Irish study shows higher mean radon concentrations for schools (93 Bq/m$^3$) than for homes (89 Bq/m$^3$) (Long and Fenton, 2011). However, information on school buildings is not available in the national census cohort data base to which the model will be applied. Thus, we did not provide regression coefficients for schools in the main model. However, the information is available in the radon database. Hence, we calculated an additional model, considering schools as additional housing type and present the backtransformed regression coefficient of schools separately.

### 2.4. Predictors considered

Factors previously proven, or suspected, to be associated with indoor radon exposure were considered in our model if data were available both in the radon database and in the national building registry, or could be derived from geographic information systems (Andersen et al., 2007; Gerken et al., 2000; Gunby et al., 1993; Hunter et al., 2009; Verdi et al., 2004; Verger et al., 1994). Such factors included geologic features determining the presence of radon, as well as others affecting the soil's gas and water permeability. The latter included: soil texture and moisture, the occurrence of subsoil horizons that restrict water penetration (impermeable layers), elevation above sea level in metres, inclination in degrees, distance to faults (in metres), degree of urbanisation (urban agglomerations, isolated cities and rural), housing type, year of construction of the building, floor of the building where the measurements were taken, and type of aquifer. The model was adjusted for the type of room, type of dosimeter, the measurement period start date and duration, and the canton where the measurements took place, as the criteria for selecting measurement sites and the housing styles and materials may have differed between cantons (Tollefsen et al., 2011).

ArcGIS 9.3 was used to extract information relating to potential determinants for each measurement coordinate, using a geological map of Switzerland with a scale of 1:500,000 (Federal Office of Topography swisstopo, 2005), as well as a soil factor map published by the Commission of the European Communities in 2000, with a scale of 1:1,000,000 (Commission of the European Communities, 2000). Data for elevation above sea level in metres and inclination from horizontal in degrees were extracted from a digital height model, based on the Swiss National Map 1:25,000 (Federal Office of Topography swisstopo, 2004). Urbanisation data were taken from the National Census of 2000 (Schuler et al., 2005).

All predictors were analysed as categorical variables, with the exception of elevation, inclination from horizontal and distance to faults, by defining the most frequently occurring category as the reference value. Missing values for predictors, if present, were coded as a separate category to avoid losing these measurements. The Alpine Molasse was reclassified into several tectonic units according to Abrecht and Tobler (2005), Bossew et al. (2008), and Labhart (1993), as given on the digital map provided by the Federal Office of Topography (Abrecht and Tobler, 2005; Bossew et al., 2008; Labhart, 1993). These units were moraines, brash, alluvial sediments, alluvial fans, upper freshwater Molasse (Langhien), lower freshwater Molasse (Aquitanien, Chattien) and upper marine Molasse (Burdigalien, Helvetien).

### 2.5. Model development

A multivariable log-linear regression model was developed to predict mean indoor radon concentration with the form:

$$\log(y) = \beta_0 + \beta_1{*}x_1 + \beta_2{*}x_2 + \beta_3{*}x_3 + \beta_n{*}x_n + E_i \quad (1)$$

where $y$ represents the mean indoor radon concentration and $x$ represents the predictors of indoor radon concentration. Outliers were detected by calculating standardized residuals and excluding those values with residuals of $<-3.5$ or $>3.5$ (Montgomery et al., 2003). In the regression analysis, data were weighted for each canton by the number of measurements per inhabitant, due to the uneven distribution of measurements between the cantons. Many more measurements for rural, less inhabited cantons were available than for more densely populated, urban cantons. Measurements from cantons with more measurements per inhabitants were therefore allocated less weight than those from cantons with fewer measurements per inhabitant.

The selection of relevant explanatory variables for the final prediction exposure assessment model was based on evidence from the available literature, the adjusted $R^2$ value, criteria for the stepwise elimination of predictors, i.e. the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), and the log-likelihood test. Analysis of variance (ANOVA) was performed to identify potentially irrelevant predictors by considering their contribution to explaining the total variance of indoor radon concentration. For variables with many categories (soil texture, tectonic unit, and type of room), categories with similar regression coefficients and content (e.g. Alpine crystalline nappes: Penninic nappes, crystalline rocks, bodies of granite rocks) were combined.

To evaluate the model, radon exposure concentrations were predicted for each measurement location and compared with the true measurement values. The agreement between measured and predicted values was depicted as a box plot and the Spearman rank correlation between the predicted versus the observed outcomes was calculated. The predicted values were categorized into three categories (50th, $>$50th–90th and $>$90th percentile) and compared with the measured values, using the weighted Kappa statistic. Measured and predicted radon concentrations were dichotomized, using a 90th percentile cut-off due to the skewed distribution of the data (Frei et al., 2009; Kühnlein et al., 2009; Schmiedel et al., 2009). To assess exposure misclassification, the sensitivity, specificity and area under the receiver operating characteristic (ROC) curve, i.e. a graph of sensitivity vs. 1-specificity, were calculated. All model evaluations were performed independently in the development dataset and the validation dataset.

All statistical analyses were carried out using STATA, Version 10.1 (StataCorp, College Station, TX, USA).

### 2.6. Sensitivity analysis

The robustness of the prediction model was assessed with various sensitivity analyses.

Firstly, the robustness of the weighted regression analysis was verified by conducting the analysis without weighting by canton

population size. Cross-validation was then performed through repeated random sub-sampling, splitting the data into two random sets - development (80% from each canton) and validation (20% from each canton). The averages of the Spearman correlation coefficient between the measured and predicted radon concentration, the weighted Kappa statistic and the sensitivity and the specificity over the splits with 500 repeats were calculated.

Secondly, the impact of outliers and extreme values was assessed through the inclusion of outliers and through Tobit regression analysis. A Tobit regression analysis treats extreme values as censored at upper and/or lower limits. The upper virtual detection limits were set to 400 Bq/m$^3$ and 1,000 Bq/m$^3$, as these are the standard legal action and threshold values, respectively (Federal Office of Public Health (FOPH), 2009). Lower limits were 10 Bq/m$^3$ and 50 Bq/m$^3$, 10 Bq/m$^3$ being the average outdoor radon concentration (Federal Office of Public Health (FOPH), 2008). Radon dosimeters have a minimum detection value of 50 Bq/m$^3$, according to Swiss legislation (Federal Office of Public Health (FOPH), 2009).

Finally, the risk of error associated with the small scale of the geological map (1:500,000) was assessed. Although geological maps of a larger scale (1:25,000) exist in Switzerland, they are not available for many alpine regions. Nine different regions across the country for which 1:25,000 tectonic maps were available were selected, equating to a total area of 1,861 km$^2$. Prediction models based on high and low resolution of the geologic maps were compared.

## 3. Results

### 3.1. Exposure model for domestic radon exposure

The geometric mean of the measured radon concentrations in living rooms was 91.2 Bq/m$^3$ and the median value was 87.4 Bq/m$^3$.

The following predictors were included in the final model: soil texture, tectonic units, housing type, degree of urbanisation, floor of the building and construction year. This model was adjusted for room type, the measurement period start date, type of dosimeter and the cantons. Table 1 shows the coefficients and 95%-confidence intervals of these predictors.

Table 2 shows the mean measured radon concentration and the interquartile range for the three predicted exposure categories. In the development data set, the Spearman rank correlation coefficient was 0.45 (95%-CI: 0.44; 0.46). Using three exposure categories, 67% radon values predicted to be in the lowest exposure category, 50% predicted to be in the middle category and 31% predicted to be in the highest exposure category were actually measured in these categories. The corresponding weighted Kappa coefficient was 0.31. When dichotomizing exposure at the 90th percentile, sensitivity was 0.31, specificity was 0.92 and the area under the ROC curve was 0.73 (95%-CI: 0.72; 0.74).

The radon prediction model indicated that school buildings were found to have 7% (95% CI: -2–17%) higher radon concentration than single family houses. When choosing apartments as reference category, school buildings were found to have 21% (10–32%) higher radon concentration.

### 3.2. Validation set

Table 3 shows the mean measured radon concentration and the interquartile range of the three predicted exposure categories. The results of the model validation are similar to those of the development set, with a Spearman correlation of 0.44 (95%-CI: 0.42; 0.46). In this validation set, 66% radon values that were predicted in the lowest exposure category and 49% predicted in the middle category were actually measured to be in these categories. Of the radon values predicted in the highest exposure category, 29% were measured in this category. The corresponding weighted Kappa coefficient was 0.30 (see Fig. 2).

For the dichotomized exposure classification, sensitivity was 0.29, specificity was 0.92 and the area under the ROC curve was 0.72 (95%-CI: 0.71; 0.74).

**Table 1**
Multivariate regression coefficients (back transformed $\beta$) and 95% confidence intervals (CI) of selected categories of variables included in the final model for predicting indoor radon concentration.[a]

| Variable | Coefficient (exp ($\beta$))[b] | (95%-CI) |
|---|---|---|
| *Soil texture*[c] | | |
| Medium grained | 1 | Reference |
| Coarse | 1.16 | (1.12; 1.19) |
| Fine grained | 0.93 | (0.88; 0.99) |
| *Geologic features* (*tectonic units*) | | |
| Moraines | 1 | Reference |
| Folded Jura | 1.61 | (1.52; 1.71) |
| Flat lying Jura | 1.37 | (1.29; 1.46) |
| Penninic nappes: sediments | 0.90 | (0.83; 0.97) |
| Alpine crystalline nappes: Penninic nappes, crystalline rocks, bodies of granit rocks | 1.48 | (1.38; 1.59) |
| East alpine nappes (crystalline) | 2.32 | (2.07; 2.60) |
| *Housing type* | | |
| Detached houses | 1 | Reference |
| Apartment house | 0.89 | (0.86; 0.92) |
| Farmhouse | 0.95 | (0.92; 0.99) |
| *Degree of urbanisation* | | |
| Rural municipalities | 1 | Reference |
| Towns and cities | 0.83 | (0.78; 0.87) |
| Suburban | 0.98 | (0.95; 1.01) |
| *Floor* | | |
| Ground floor | 1 | Reference |
| Basements (inhabited) | 1.34 | (1.24; 1.46) |
| Raised ground floor | 0.76 | (0.65; 0.90) |
| First floor | 0.85 | (0.82; 0.88) |
| Second floor and above | 0.75 | (0.68; 0.81) |
| *Year of construction*[d] | | |
| Until 1918 | 1 | Reference |
| 1918–1945 | 0.99 | (0.95; 1.03) |
| 1946–1970 | 0.79 | (0.77; 0.82) |
| 1971–1990 | 0.70 | (0.67; 0.73) |
| 1991–2009 | 0.69 | (0.63; 0.76) |

[a] Adjusted for type of room, type of dosimeter, the measurement period start date and the cantons where the measurements took place.

[b] How to interpret the coefficient of the model? After adjusting for type of room, type of dosimeter, the measurement period start date and the cantons, the predicted mean radon concentration is 94.7 Bq/m$^3$ when all factors are set to the reference value. The reference values are: living room of a flat on the ground floor of a detached house, constructed before 1918, with natural floors, situated in a rural municipality in a region with moraines and medium grained soil. By multiplying the factors, the estimation of the indoor radon concentration for each scenario can be calculated. Example: mean radon concentration for a room on the first floor of a detached house, constructed in 1972 and situated in a rural municipality in a region of the Alpine crystalline nappes with coarse soil: 0.85*1*0.70*1*1.48*1.16*94.7 = 96.7 Bq/m$^3$ (considers adjustment for type of room, type of dosimeter, beginning of the measurement period and cantons). Note that mean concentration refers to a geometric means due to the back transformation of logarithms.

[c] A selection of categories is presented here only. We did exclude the following tectonic units: brash, Upper and Lower Freshwater Molasse (Langhien, Aquitanien), alluvial sediments, Upper Marine Molasse (Burdigalien), Lower Freshwater Molasse (Chattien), alluvial fans, peat within the tectonic unit Molasse, Helvetic nappes, southern alpine nappes: sediments, quaternary deposits, east alpine nappes: sediments.

[d] Categories created according to the national building registry.

**Table 2**
Mean radon concentration, median and interquartile range (IQR) for the three exposure categories: development set.

| Exposure | Measurement | | |
|---|---|---|---|
| | Geometric mean (Bq/m$^3$) | Median (Bq/m$^3$) | IQR (Bq/m$^3$) |
| Low (<50%) | 66.0 | 66.1 | 39.9–110.9 |
| 50–90% | 126.0 | 118.7 | 69.4–214.9 |
| high (>90%) | 218.7 | 201.6 | 108.0–426.9 |

**Table 3**
Mean radon concentration, median and interquartile range (IQR) for the three exposure categories: validation set.

| Exposure | Measurement | | |
|---|---|---|---|
| | Geometric mean (Bq/m$^3$) | MEDIAN (BQ/M$^3$) | IQR (Bq/m$^3$) |
| low (<50%) | 66.0 | 66.1 | 39.2–109.8 |
| 50–90% | 126.3 | 121.0 | 68.5–211.8 |
| high (>90%) | 214.5 | 200.6 | 103.4–428.3 |

### 3.3. Sensitivity analysis

The results of all sensitivity analyses were similar compared to the main analysis. Applying different approaches towards extreme values and outliers resulted in Spearman correlations ranging from 0.44 to 0.45. Regression analyses without weights produced a Spearman rank correlation of 0.45 in the development set and 0.45 in the validation set. In all analyses, sensitivities were between 0.29 and 0.32 and specificities were between 0.92 and 0.93. The weighted Kappa statistics were between 0.29 and 0.31. These figures were virtually the same for the development and validation sets. The area under the ROC curve was between 0.72 and 0.73.

The explained variance ($R^2$) of the prediction model based on high resolution tectonic maps (1:25,000) and encompassing nine selected regions across the whole country was 40.7%, which was considerably higher than the $R^2$ of the nationwide model. However, a model of the same area based on tectonic maps with a smaller resolution (1:500,000) yielded a similar $R^2$ (41.1%).

## 4. Discussion

Our prediction model indicates that indoor radon concentrations are higher in regions with crystalline rocks (Alpine regions) and karst formations (Jurassic regions). Radon levels are also increased in regions with a predominantly coarse soil texture compared to those with a fine soil texture. Lower radon concentrations were estimated in towns and cities compared to rural communities, and also for apartments compared to single family houses. Decreased radon levels were predicted for newer buildings and for upper floors. The sensitivity analyses clearly demonstrated that the prediction model is robust and not influenced by extreme values or by the estimation procedure.

Distinct differences in measured radon levels between the three predicted exposure categories were found. This was also the case during validation with an independent dataset which was not used for model development. The performance of the predictions was virtually the same in the validation dataset as in the development dataset, indicating that the model is not over fitted and that the estimated coefficients are robust.

Nevertheless, the proportion of variance explained by the model was relatively low and there was considerable overlap between exposure groups, as expressed by the relatively low Kappa statistics and the low model sensitivity. Only about one third of all predicted radon values in the highest exposure category were actually measured within that category.

Average Swiss radon values are higher than in other countries (Table 4). On the other hand, the adjusted $R^2$ for Switzerland was lower than the $R^2$ in the prediction models for these countries (Table 4). Possible reasons for the low proportion of variance explained by the prediction model include inaccurate input data and the absence of data about relevant predictors, such as room ventilation or type of fundament. Such detailed predictor data would have been useful. Nevertheless, the most important factors according to the literature were included, namely geology and soil permeability (Nazaroff, 1992; Nero and Nazaroff, 1984; Tollefsen et al., 2011).

Regarding input data, the map of tectonic units was scaled at 1:500,000 whilst the soil data map was 1:1,000,000 (Commission of the European Communities, 2000; Federal Office of Topography swisstopo, 2005). The former has an inaccuracy of 0.1–0.3 mm, according to the Federal Office of Topography, meaning that the inaccuracy of the geological map is between 50 m and 150 m. In addition, an inaccuracy between 100 m and 300 m for the soil map is expected if the same inaccuracy is assumed as for the maps, produced by the Federal Office of Topography. It is, therefore, possible that sampling points may have been misclassified in terms of geological unit and soil texture. However, our sensitivity analysis comparing the effect of map resolution suggested that a higher map resolution would not noticeably increase the explained variability of the prediction model. No evidence was found for map resolution limiting the accuracy of predictions.

The geology of the Swiss Alps is particularly complex and not well understood, such that the tectonic categories used for this prediction model are a simplification of this complex system (Labhart, 1993). This may have increased the likelihood of exposure misclassification, when compared to countries such as Denmark where the explained variance of the model ($R^2$) was 40%. Denmark probably has a less complex geological system with lower small scale variation of radon levels. This may have resulted in the higher $R^2$ value for the prediction model of indoor radon concentrations in Danish households when compared to our prediction model (Andersen et al., 2007).

Interestingly, our sensitivity analysis demonstrated that, regardless of the resolution of the geologic maps, the explained variance of the model for the selected regions was considerably higher (approx. 41%) than for the nationwide model (approx. 20%).

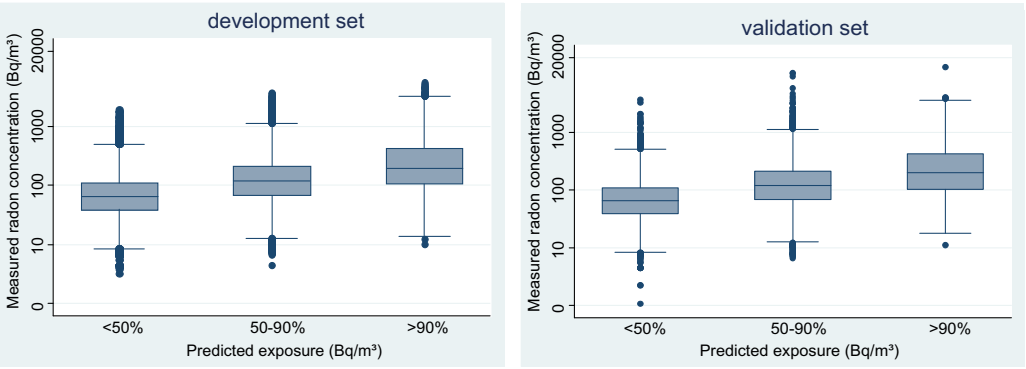


**Fig. 2.** Distribution of measured domestic radon concentration in the three predicted exposure categories for the model development dataset, left: development set, right: validation set.

**Table 4**
Comparison with past radon exposure models.

| | Our study | Danish study[a] 2007 | British study[b] 1993 | British study[c] 2009 | German study[d] 2000 | French study[e] 1994 | Italian study[f] 2004 |
|---|---|---|---|---|---|---|---|
| Radon levels | | | | | | | |
| GM[g] | 91.2 Bq/m$^3$ | 64 Bq/m$^3$ | 14.9 Bq/m$^3$ | 61.7 Bq/m$^3$ | | 52 Bq/m$^3$ | |
| median | 87.4 Bq/m$^3$ | | | | West: 40 Bq/m$^3$, East: 56 Bq/m$^3$ | 47 Bq/m$^3$ | |
| (Adjusted) $R^2$ | 20% | 40% | 22% | 29% | 15–31% (different models calculated) | 28% | 57%, 97% for 2 models on municipality level indicated only |
| $n$ (total)[h] | 39,276 buildings 44,631 measurements | 3,874 buildings | 2,093 buildings | 39,823 buildings | Unknown | 1,548 measurements | 3,763 measurements |
| Predictors | Housing type | Housing type | Housing type | Housing type | Housing type | Dwelling type | Floor |
| | Floor | Floor | Floor | Floor | Floor | Floor | Building material |
| | Year of construction | Building material | Building material | Floor type | Year of construction | Building material | Year of construction |
| | Type of room | Number of floors | Window isolation | Year of construction | Window isolation | Season | Type of room |
| | Tectonic units | % top floor inhabited | Draught proofing | Window isolation | Type of construction | Departments | Fixtures quality |
| | Soil texture | % housing area with basement | Floor type | Draught proofing | Basement type | | Municipalities |
| | Degree of urbanisation | Row housing | Bedroom window position | Ownership | Basement insulation | | Season |
| | Cantons | Soil types | Rock type | Geological units | Heating system | | Contact with soil |
| | Type of dosimeter | Geographical regions | | | Ventilation frequency | | Altitude |
| | Beginning of measurement | | | | Geological radon potential | | Slope |
| | | | | | | | lodes |

[a] Andersen et al., 2007.
[b] Gunby et al., 1993.
[c] Hunter et al., 2009.
[d] Gerken et al., 2000.
[e] Verger et al., 1994.
[f] Verdi et al., 2004, Study carried out in the South Tyrol.
[g] GM = geometric mean; except from the French study (Verger et al., 1994) and the studies from the UK from 1993 (Gunby et al., 1993) and 2009 (Hunter et al., 2009), the geometric means and the medians are indicated for living rooms only.
[h] Some of the studies listed did not indicated the number of measurements used for their prediction models, but instead the number of buildings where the measurements were carried out.

The model for the selected regions was based on only 1,107 measurements. This could indicate that models based on smaller samples sizes are more likely to produce higher $R^2$ values as was seen in an Italian model (Table 4) (Verdi et al., 2004).

The strength of this study is that a high number of measurements from across the whole country were available (Table 4). This comparatively high sampling density in Switzerland is referred to in a study investigating the number of measurements within different European countries (Tollefsen et al., 2011). The predictors included in our final model had all been identified as important in other studies of radon prediction models, except for 'degree of urbanisation' which had not been previously considered (Table 4). A German study found higher radon values for detached houses compared to multiple dwellings and lower radon values for the upper floor compared to lower floors (Gerken et al., 2000), similar to our study and a study conducted in the UK in 2009 (Hunter et al., 2009). Also an earlier study from the UK was in line with our findings as it found higher radon concentrations in detached houses or in regions with crystalline rocks, although Britain is geologically very different to Switzerland and different categories for housing types were used (Gunby et al., 1993). Regression coefficients for soil characteristics are not reported in other studies, but our results for soil texture confirm what has been described with theoretical equations for soil texture and soil permeability (Nazaroff, 1992; Nero and Nazaroff, 1984; Tanner, 1980).

The similar model performance for both the validation and development datasets demonstrates the model's general applicability. The relatively low proportion of variance explained by the model is of concern. It is, however, important to note that our prediction error is expected to follow a mostly Berkson error type (Heid et al., 2004; Steenland et al., 2000). Berkson error occurs when predictions are assigned on a group level with some within-group variance, but the error does not affect group assignment (e.g. determination of housing type, degree of urbanisation, etc.) The occurrence of Berkson error implies that the regression coefficients of the prediction models are unbiased and that the mean of the true but unobserved radon values corresponds to the predicted value (Armstrong, 1998; Steenland et al., 2000). Berkson error does, however, lead to greater standard errors of association estimates (Armstrong, 1998).

Possible exposure misclassification from so-called classical errors must also be considered. This can occur if group assignment is incorrect which, in our case, could occur in relation to the tectonic units with their low spatial resolution. Exposure misclassification following a classical error is unlikely to create a spurious association if none exists in reality, but would shift regression coefficients towards unity if an association were present. In this case, regression calibration can be applied. Regression calibration considers a statistical model of the association between the true, but unobserved, radon values and the predicted radon values. The estimates from the calibration model are then used to correct the regression coefficients (Bartlett et al., 2009; Guolo, 2008; Thurigen et al., 2000). The data from this study will be useful for such a regression calibration.

## 5. Conclusion

Based on almost 36,000 measurements from the Swiss radon database, a model was developed for predicting indoor radon concentration. This prediction model was validated with almost 9,000 independent radon measurements and found to be robust. Nevertheless, random exposure misclassification was relatively high and must be taken into account in future applications of the model.

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## Article 2: Prediction of residential radon exposure of the whole Swiss population: comparison of model-based predictions with measurement based predictions

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# Prediction of residential radon exposure of the whole Swiss population: comparison of model-based predictions with measurement-based predictions

**Abstract** Radon plays an important role for human exposure to natural sources of ionizing radiation. The aim of this article is to compare two approaches to estimate mean radon exposure in the Swiss population: model-based predictions at individual level and measurement-based predictions based on measurements aggregated at municipality level. A nationwide model was used to predict radon levels in each household and for each individual based on the corresponding tectonic unit, building age, building type, soil texture, degree of urbanization, and floor. Measurement-based predictions were carried out within a health impact assessment on residential radon and lung cancer. Mean measured radon levels were corrected for the average floor distribution and weighted with population size of each municipality. Model-based predictions yielded a mean radon exposure of the Swiss population of 84.1 $Bq/m^3$. Measurement-based predictions yielded an average exposure of 78 $Bq/m^3$. This study demonstrates that the model- and the measurement-based predictions provided similar results. The advantage of the measurement-based approach is its simplicity, which is sufficient for assessing exposure distribution in a population. The model-based approach allows predicting radon levels at specific sites, which is needed in an epidemiological study, and the results do not depend on how the measurement sites have been selected.

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Key words: Exposure assessment; Model-based predictions; Measurement-based predictions; Indoor radon concentration; Household predictions; Population-based predictions.

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**Practical Implications**

Accurate assessment of radon exposure at population level is important for health impact assessments. Radon measurements are the gold standard to determine radon levels in a specific building. However, population radon exposure assessment may be biased, if measurement sites are not selected in a representative way. This study demonstrates that a nationwide prediction model is suitable for assessing radon exposure at population level. The model-based approach is unlikely to be affected by the way the measurement sites are selected. Uncertainties of the model-based approach depend on the underlying regression model and not on the number of available measurements per community. Further, the model-based approach allows estimating radon levels in specific subgroups (e.g., age-groups, regions, or building age) and is useful for identifying buildings with a high radon risk in a systematic way.

## Background

Radon plays an important role for human exposure to natural sources of ionizing radiation. Radon is a nuclide of a long radioactive decay chain, originating from uranium, a naturally occurring element in granites and metamorphic rocks (Ball et al., 1991; Gillmore et al., 2005; Gunderson, 1992). Radon emanates from soils and tends to concentrate inside buildings. Worldwide, radon is responsible for 50% of the effective total annual ionizing radiation dose (1.2 mSv/year; Charles, 2001). In different European countries (Austria,

France, Germany, United Kingdom), radon is estimated to be responsible for 30% to 50% (0.9–3 mSv/year) of the effective total annual ionizing radiation dose of the population (Baysson et al., 2004; Charles, 2001; Friedmann, 2005; Hughes et al., 2005). For Switzerland, the Swiss Federal Office of Public Health (FOPH) estimated that radon is responsible for 60% of the effective total annual ionizing radiation dose (3.6 mSv) of the Swiss population (FOPH, 2011).

In the framework of a census-based cohort study of indoor radon concentrations and childhood cancer, we developed a multivariable log-linear regression model to predict residential radon concentration in each household in Switzerland (Hauri et al., 2012). Like other authors, we demonstrated with our model that radon levels inside of buildings vary and depend on geology, soil permeability, and on building characteristics that are type of building, building age, and floor (Andersen et al., 2007; Gerken et al., 2000; Gunby et al., 1993; Hauri et al., 2012; Hunter et al., 2009; Verdi et al., 2004; Verger et al., 1994). We concluded that the model was robust and appropriate for predicting radon level exposure of the Swiss population in epidemiological research (Hauri et al., 2012). Nevertheless, some exposure misclassification and regression to the mean was unavoidable and should be taken into account in applications of the model.

Accurate assessment of radon exposure at population level is important for health impact assessments. Previously, the number of lung cancer deaths, attributable to residential radon concentration, was estimated for Switzerland, using a measurement-based exposure assessment method (Menzler et al., 2008). This method consisted in aggregating measurements at municipality level considering floor and population distribution in around 2500 Swiss municipalities and based on these estimates estimating average radon levels for all 26 Swiss cantons. In our study, we combined our nationwide radon prediction model with all households and persons from the national census database. The objective was to predict radon levels for all households and persons in Switzerland at individual level for future application in an epidemiological study.

The aim of this article was to compare radon exposure assessment of the Swiss population using nationwide model-based predictions with a measurement-based exposure assessment method. An objective consisted in presenting the results from our exposure assessment according to different regions, housing characteristics, and age-group.

## Methods

### Model-based predictions

The model is described in detail in (Hauri et al., 2012). In brief, 44 631 measurements from the Swiss radon database, collected between 1994 and 2004 homogeneously over Switzerland by the FOPH, could be used for the model development. Coefficients of the log-linear regression model were estimated based on 80% of the measurements and independently validated with the remaining 20% of the measurements that were collected at the same time and in the same manner but not used for model development. The following predictors were found to be relevant and included in the model: tectonic units, soil texture, degree of urbanization, building type, year of construction and floor as well as type of room, type of dosimeter, measurement year, and canton. The model explained 20% overall variability (adjusted $R^2$) and was demonstrated to be robust and not overfitted through validation with an independent dataset: Its performance was almost the same in the validation set as in the development set.

For predicting the radon exposure of the Swiss population, we extracted spatial data, that is, data on geologic features, soil data, and degree of urbanization from digital maps for each building, using ArcGIS. Data on the tectonic units were available from the geologic map, scale 1:500 000, issued in the year 2005 from the Federal Office of Topography Swisstopo (2005). Soil data were published by the Commission of the European Municipalities and were available on a scale of 1:1 000 000, published in the year 2000 (Commission of the European Communities, 2000). Data on the degree of urbanization are available per municipality in the census data of the year 2000 (Schuler et al., 2005).

Building factors were extracted from the Swiss National Cohort (SNC). The SNC is a nationwide longitudinal research platform, linking census data from the censuses 1990 and 2000 and additionally linking them with mortality and emigration data (Bopp et al., 2009). It contains data from all buildings, households, and all people living in Switzerland from the national census 1990 and 2000 (Bopp et al., 2009). All buildings in the census are geo-coded where the building coordinate denominates approximately the building midpoint. For this analysis, data were obtained from the census conducted in the year 2000. For the model-based predictions, year of building construction, floor of the household, and housing type were extracted from the SNC. The latter was defined based on the number of floors, the floor level of the households, the number of housing units/flats, and the information if the buildings were used as residential buildings or for other purposes including farming houses.

In the original model, floor was used as categorical variable (Hauri et al., 2012). For comparison with the measurement-based assessment, we decided to re-estimate the original model coefficients using floor level as a continuous predictor instead of a categorical one. The census database contains households with no floor information ($n$ = 164 316). We assumed that sleeping

rooms are situated on first floors and the other rooms most frequently on ground floors in detached houses and farming houses. In this case, we indicated the floor of households with missing floor information ($n$ = 40 636) as 0.5. For the other households with missing floor information ($n$ = 123 680), we replaced the missing values, using the multiple imputation technique for univariate cases (Van Buuren et al., 1999). Multiple imputation allows estimating missing values for predictors of interest by existing data, whereas we used predictors that might be related to the predictor of interest (Van Buuren et al., 1999). In the case of this study, multiple imputation was based on building type, age of building, number of floors, and number of housing units in each building.

Of a total of 3 181 550 households with 7 280 246 inhabitants, we excluded uninhabited households, households in emergency shelters, or collective household (i.e., nursing homes, approved schools, prisons, dormitories, residential schools; Figure 1). We also excluded households if building coordinates were inaccurate (Figure 1) or if they were available in hectare resolution but not in square meter resolution. Coordinates were judged to be inaccurate if the municipality name in the database did not match with the coordinates. In addition, only 0.7% of all inhabited households ($n$ = 22 700) are situated in basements. As the measurement-based exposure assessment excludes basements (Menzler et al., 2008), we also excluded households in basements for the model-based predictions in this article. In total, we used 2 997 742 households for the predictions, inhabited by 6 764 091 individuals in the year 2000.

Radon levels in each household were calculated by means of the multivariable log-linear regression model (Hauri et al., 2012). The radon database also contained measurement-related information, that is, information on the type of room where the measurements were carried out, information on the type of dosimeter used for the measurements, and the measurement period start date (Hauri et al., 2012). As mean measured radon values varied depending on these factors, we adjusted the radon model for these factors (Hauri et al., 2012). However, information on these factors is not contained in the SNC. Predictions in each household therefore referred to the bedrooms because 55% of the time spent indoors is spent in sleeping rooms (Darby et al., 1998). Predictions in each household referred to Gammadata dosimeter because they were judged to be most reliable in a measurement study of the Swiss Paul Scherrer Institute in 2006 (Butterweck and Schuler, 2006). We predicted radon levels for the most recent period from 2001 to 2004.

Prediction of the radon exposure of the population was obtained by combining the apartment predictions with the population distribution obtained from the census data.

### Measurement-based exposure assessment method

The measurement-based exposure assessment, the results of which can be defined as measurement-based predictions, considered measurements carried out between 1981 and the beginning of 2004 in Switzerland (Menzler et al., 2008). The authors calculated mean radon concentration for each municipality where measurements were carried out. Radon values of each building were floor corrected according to the average floor distribution within a municipality and subsequently averaged by dwelling and then population weighted with the population size of each municipality. Based on these calculations, arithmetic and geometric means of radon levels for the population of each canton and for Switzerland were estimated.

### Statistical analyses

We carried out predictions for all households and individuals of each household. In terms of the households, we summarized the results for different factors such as

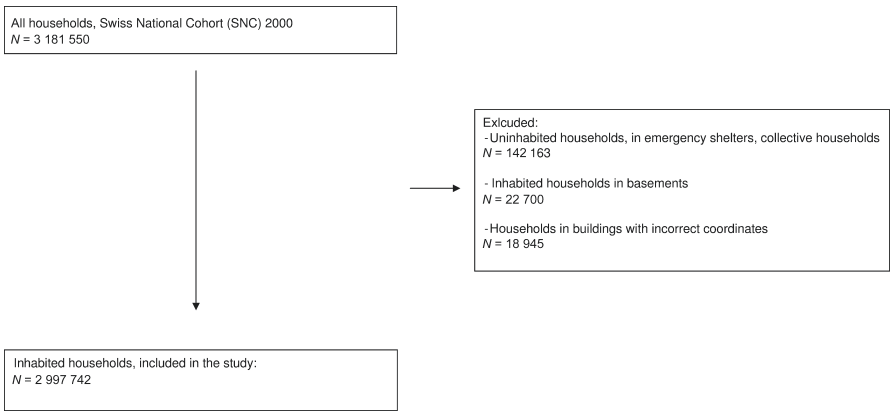


**Fig. 1** Selection procedure of the households, considered for the predictions

regions, degree of urbanization, year of construction, building types, and floor level. We calculated mean radon concentrations and presented the data distribution of the predictions (range, 10th, 50th, and 90th percentile). Arithmetic mean values are considered relevant in this context because they represent the most common dose model in this area of research: a linear cumulative dose without threshold. For the calculation of arithmetic means, we multiplied the back-transformed predictions of the log-linear model with a correction factor that is defined as

$$e^{\mathrm{rmse}^2/2} \quad (1)$$

where 'rmse' equals to the residual standard deviation (Newman, 1993). This calculation was made to prevent transformation bias.

We also present geometric mean values without using a correction factor when back transforming the data because it is argued from a statistical point of view that geometric means represent better the central tendency of skewed distributed data by giving similar weight to all observations (Baccarelli et al., 2005; Blackwood, 1992; Kirkwood and Sterne, 2003; Limpert et al., 2001; Parkhurst, 1998).

For the comparison of model-based predictions with the measurement-based predictions, we calculated averages for all 26 cantons for the different approaches. The same was done when comparing both the model-based predictions and the measurement-based predictions with averages of measurements. For the latter approach, we also compared the spatial distribution of households, selected for radon measurements with the spatial distribution of the households listed in the national census 2000, and calculated an indicator for the representativeness of the measurement sites by dividing the proportion of measured detached houses in a canton with the proportion of all detached houses. Because it is well known that radon levels are higher in detached houses, the degree of over-representation of detached houses is expected to indicate the degree of high-risk measurement strategy. We then compared predicted and measured radon values as a function of the measurement selection strategy for different cantons.

Agreement of cantonal arithmetic means, calculated with these three approaches, was assessed by calculating Spearman correlations. When comparing the model-based predictions with averages of measurements, it was further possible to assess agreement of arithmetic means at municipality level for almost 2500 municipalities. We also compared predicted and measured radon values per community as a function of the number of measurements carried out in each municipality.

We finally assessed the model's capability to predict peak values by comparing predicted values with measured values for the corresponding rooms. For this purpose, we indicated the proportion of measurement and predictions that exceeded peak values at the lower (<10 $Bq/m^3$) and the top end (>300 $Bq/m^3$). A value of 10 $Bq/m^3$ corresponds to the average outdoor radon concentration in Switzerland (FOPH, 2008). According to the World Health Organisation (WHO), a value of 300 $Bq/m^3$ should not be exceeded. Constructional actions are recommended already above a threshold of 100 $Bq/m^3$ (WHO, 2009). We thus indicated the proportion of households exceeding 100 and 300 $Bq/m^3$, respectively, as well as the percentage of persons, living in households exceeding 100 and 300 $Bq/m^3$. We also indicated the proportion of municipalities, where mean radon concentration over dwellings exceeds 200 $Bq/m^3$ because such a municipality is currently declared as high-risk municipality in Switzerland (FOPH, 2011).

We carried out all statistical analyses using STATA version 10.1 (StataCorp, College Station, TX, USA).

## Results

### Model-based predictions: household predictions

Average model-based predicted radon concentration for all Swiss households (arithmetic mean) was 82.1 $Bq/m^3$, ranging from 0.4 to 464.9 $Bq/m^3$. The geometric mean was 50.9 $Bq/m^3$.

According to the predicted values for all Swiss households, 9% of the municipalities are high radon risk municipalities (Figure 2). In general, predicted radon concentrations were higher for households in the Jurassic regions and the central, southern, and eastern Alpine regions compared to households in the Central Plateau (Figure 2, Table 1). Households with predicted radon concentrations above 100 $Bq/m^3$ were found in the Alps and the Jurassic region, whereas around 1% of all households in these regions even exceed 300 $Bq/m^3$ (Table 1). The eight cantons (of 26 cantons) where average predicted radon concentration of all households was above 100 $Bq/m^3$ (arithmetic mean) are mainly situated in the Alps and in the Jurassic region (Table S1). The canton with households with the highest mean predicted radon concentration was found in the Alps (Glarus) and the one with the lowest mean predicted radon concentration of all cantons in the Central Plateau (Geneva; Table S1).

Within the regions, we predicted lower radon concentrations for households in areas with soils more likely to be sealed (cities and suburban areas) compared to those with soils less likely to be sealed (rural municipalities; Table 1). We also predicted lower radon concentrations for households in newer buildings (built after 1945) in apartments compared to detached houses and farms and in households situated in upper floors (Table 1).

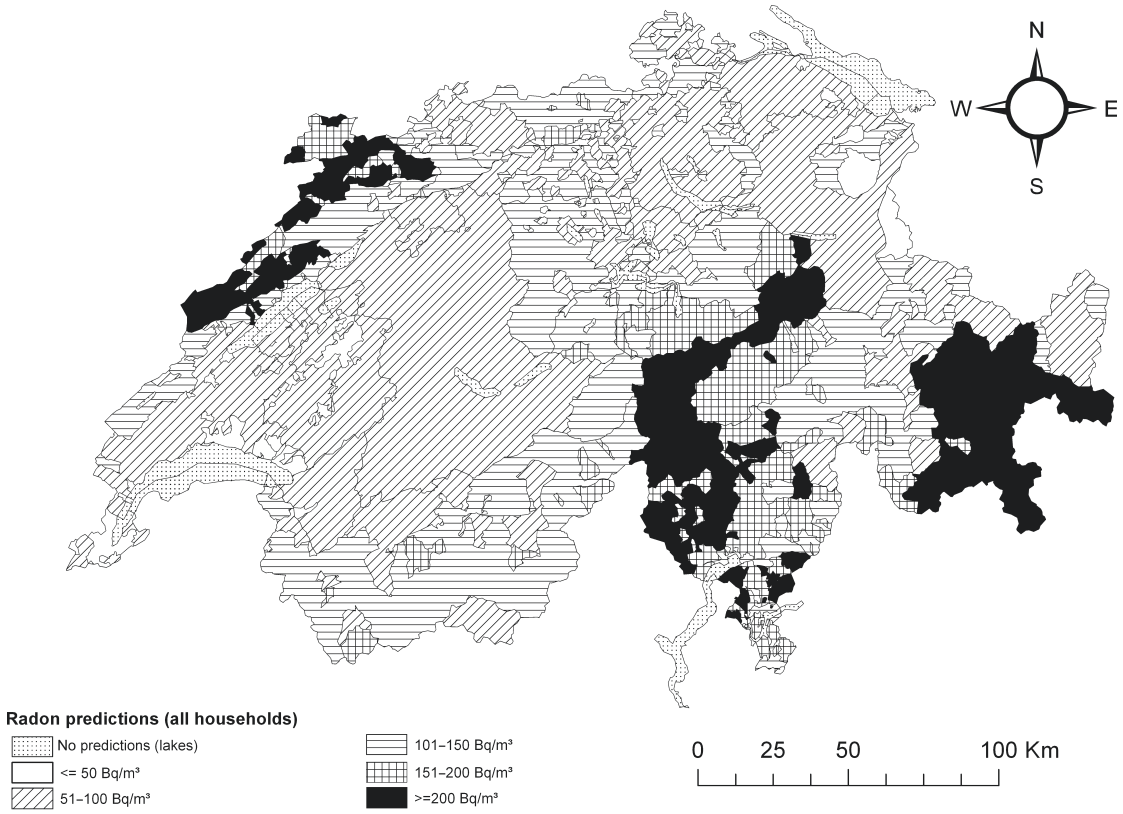


**Fig. 2** Model-based predictions: area predictions for the year 2000: indoor radon concentrations for all households [municipality averages (arithmetic means)], based on a prediction model that takes geology, soil, and building characteristics into account. Digital map of municipalities (2001) was kindly provided by the Swiss Federal Statistical Office, GEOSTAT

### Model-based predictions: population predictions

The Swiss population was on average (arithmetic mean) exposed to a radon concentration of 84.1 Bq/m$^3$, ranging from 0.44 to 464.9 Bq/m$^3$. Geometric mean was 52.5 Bq/m$^3$ (Table 2). Predicted radon concentrations varied only little between age-groups (Table 2).

### Comparison of model-based predictions with the measurement-based exposure assessment and measurements

The measurement-based approach yielded a geometric mean of 51 Bq/m$^3$ and an arithmetic mean of 78 Bq/m$^3$ (Table 3). Measurement-based predictions were somewhat lower for most cantons than model-based predictions. The model- as well as measurement-based predictions were considerably lower than average measured radon levels per canton (Table 3). Measurements were more frequently carried out at sites with a higher likelihood for high radon levels, that is, areas with crystalline bedrock, coarse soils, detached houses, or older buildings than the average found in the national census 2000 (Table S2). Figure 4 shows that the ratio between measurement-based and model-based predictions was higher for cantons where measurement sites were selected in a nonrepresentative way. The more representative measurement sites were selected in a canton, the closer was the ratio to unity. Interestingly, ranking of the cantonal average radon levels was relatively similar for all three approaches. Spearman correlation between model-based and measurement-based predictions of arithmetic means at cantonal level was 0.70 (95% CI: 0.41; 0.86). Spearman correlation of arithmetic means between model-based predictions and averages of measurement was 0.84 (95% CI: 0.65; 0.93).

At the municipality level, agreement was lower. Spearman correlation of arithmetic means between model-based predictions and averages of measurement was 0.46 (95% CI: 0.43; 0.49). Figures 2 and 3 depict arithmetic means of indoor radon concentration at municipality level and indicate that areas with higher measured radon concentrations (i.e., namely the Alps and the Jurassic region) were also identified as such with the model-based predictions. However, variance of the ratio between measured and predicted values tended to decrease with increasing number of measurements per municipality (Figure 5). Uncertainty was substantial if <5 measurements per community were available.

When applying predictions to the rooms where the measurements took place, we found 2.4% of the predicted values being above 300 Bq/m$^3$ and none below 10 Bq/m$^3$. Ten percent of all measurements were above

**Table 1** Model-based predictions: household-based predictions for the year 2000[a]

| | Households (*n*) | Geometric mean (Bq/m$^3$) | Arithmetic mean (Bq/m$^3$) | 10th percentile (Bq/m$^3$)[b] | 50th percentile (Bq/m$^3$)[b] | 90th percentile (Bq/m$^3$)[b] | >100 Bq/m$^3$ (%) | >300 Bq/m$^3$ (%) |
|---|---|---|---|---|---|---|---|---|
| All households | 2 997 742 | 50.9 | 82.1 | 37.8 | 73.4 | 136.2 | 24.8 | 0.2 |
| I. Households: different regions | | | | | | | | |
| Central Plateau | 1 849 530 | 43.9 | 68.5 | 34.0 | 65.3 | 106.0 | 13.5 | 0 |
| Jurassic region | 327 647 | 80.0 | 124.1 | 66.2 | 110.6 | 205.1 | 59.7 | 0.5 |
| Alpine region | 284 784 | 78.6 | 126.3 | 55.7 | 113.2 | 217.0 | 57.7 | 1.1 |
| II. Degree of urbanization of the municipalities where the households are situated | | | | | | | | |
| Urban | 966 400 | 39.5 | 63.8 | 29.1 | 57.1 | 103.4 | 11.0 | <0.01 |
| Suburban areas | 1 289 443 | 53.4 | 84.1 | 42.3 | 77.6 | 133.9 | 26.5 | 0.1 |
| Rural | 716 285 | 65.1 | 102.0 | 52.9 | 89.6 | 169.5 | 39.8 | 0.5 |
| III. Year of construction of the buildings where the households are situated | | | | | | | | |
| <1918 | 539 457 | 64.3 | 102.7 | 49.7 | 89.5 | 169.4 | 41.0 | 0.7 |
| 1919–1945 | 331 308 | 61.4 | 98.0 | 47.6 | 86.3 | 166.0 | 37.3 | 0.2 |
| 1946–1970 | 931 432 | 47.7 | 77.0 | 33.9 | 69.5 | 127.5 | 21.8 | 0.03 |
| 1971–1990 | 833 102 | 45.4 | 72.1 | 35.0 | 66.0 | 114.9 | 16.4 | <0.01 |
| 1991–2000 | 362 443 | 46.7 | 73.0 | 37.0 | 67.3 | 114.0 | 16.2 | <0.01 |
| IV. Different building types where the households are situated | | | | | | | | |
| Detached houses | 882 876 | 67.1 | 103.2 | 56.2 | 92.9 | 165.7 | 41.8 | 0.2 |
| Farming houses | 141 092 | 67.6 | 103.3 | 59.6 | 92.4 | 156.2 | 41.1 | 0.6 |
| Apartments | 1 390 863 | 43.4 | 69.2 | 33.3 | 63.3 | 109.5 | 14.0 | 0.04 |
| V. Households on different floor levels | | | | | | | | |
| Ground floor | 483 457 | 64.7 | 99.7 | 55.2 | 88.7 | 157.2 | 37.2 | 0.4 |
| First floor[c] | 1 410 800 | 60.9 | 94.1 | 51.1 | 83.8 | 148.9 | 32.8 | 0.2 |
| Second floor | 516 082 | 45.9 | 70.8 | 39.4 | 63.7 | 111.4 | 13.8 | 0.02 |
| Third floor and above | 587 403 | 29.7 | 48.7 | 20.9 | 42.6 | 81.7 | 5.2 | 0 |

[a]Predictions account for the predictors for which the model was adjusted for, that is, type of room, type of dosimeter, the time, when the measurements started, and the cantons where the measurements took place. Thus, these predictions refer to sleeping rooms for the period between 2000 and 2004. They also refer to Gammadata as type of dosimeter.
[b]Empirically defined from the distribution of the predicted arithmetic means.
[c]Including raised ground floors.

**Table 2** Model-based predictions: population predictions for the year 2000[a]

| | Persons (*n*) | Geometric mean (Bq/m$^3$) | Arithmeticmean (Bq/m$^3$) | 10th percentile (Bq/m$^3$)[b] | 50th percentile (Bq/m$^3$)[b] | 90th percentile (Bq/m$^3$)[b] | >100 Bq/m$^3$ (%) | >300 Bq/m$^3$ |
|---|---|---|---|---|---|---|---|---|
| All age-groups | 6 764 091 | 52.5 | 84.1 | 39.7 | 75.6 | 138.4 | 26.4 | 0.2 |
| Children (0–14) | 1 189 381 | 53.9 | 85.7 | 42.0 | 77.5 | 139.1 | 27.5 | 0.2 |
| 0–4 years | 368 531 | 52.8 | 84.1 | 40.7 | 75.9 | 137.1 | 26.1 | 0.2 |
| 5–14 years | 820 850 | 54.4 | 86.4 | 42.6 | 78.4 | 140.1 | 28.1 | 0.2 |
| 15–29 years | 1 204 166 | 51.4 | 82.2 | 39.0 | 74.1 | 135.0 | 24.9 | 0.1 |
| 30–49 years | 2 148 762 | 52.3 | 83.5 | 40.2 | 75.1 | 136.6 | 25.7 | 0.1 |
| 50–64 years | 1 226 962 | 52.3 | 84.1 | 39.4 | 75.5 | 139.3 | 26.4 | 0.2 |
| $\geq$65 years | 994 820 | 52.7 | 86.0 | 37.9 | 76.3 | 144.6 | 28.7 | 0.2 |

[a]Predictions account for the predictors for which the model was adjusted for, that is, type of room, type of dosimeter, the time, when the measurements started, and the cantons where the measurements took place. Thus, these predictions refer to sleeping rooms for the period between 2000 and 2004. They also refer to Gammadata as type of dosimeter.
[b]Empirically defined from the distribution of the predicted arithmetic means.

300 Bq/m$^3$, and 1.2% of all measurements were below 10 Bq/m$^3$.

## Discussion

According to our nationwide model-based predictions, mean radon exposure of the Swiss population was 8% higher than obtained from the measurement-based predictions. At the cantonal level, ranking of the radon levels was relatively similar for both approaches, whereas on the community level, differences between model-based and measurement-based predictions increased when less measurements were available per community.

Our model-based predictions indicated differences in radon exposure according to geographical region and housing characteristics, but only small differences in radon exposure between age-groups.

A strength of the model-based indoor radon assessment is that it allows the prediction of indoor radon concentrations for each individual at each residence. Conducting measurements within each residence would be impractical due to the high costs and may introduce bias because not everybody would agree to carry out

**Table 3** Comparison: model-based predictions with measurement-based predictions and measurements

| | Model-based predictions (Bq/m$^3$)[a] | | Measurement-based predictions (Menzler, 2008; Bq/m$^3$)[b] | | Arithmetic mean of measurements only 1994–2004 (Bq/m$^3$)[c] | |
|---|---|---|---|---|---|---|
| Cantons | Geometric mean | Arithmetic mean | Geometric mean | Arithmetic mean | Geometric mean | Arithmetic mean |
| Switzerland | 52.5 | 84.1 | 51 | 78 | 87.1 | 157.8 |
| Geneva | 22.5 | 35.1 | 19 | 29 | 39.3 | 55.9 |
| Fribourg | 33.9 | 50.2 | 40 | 50 | 44.7 | 60.0 |
| Vaud | 35.2 | 53.2 | 45 | 76 | 60.5 | 112.9 |
| Thurgau | 38.7 | 56.7 | 51 | 75 | 56.3 | 81.0 |
| Zug | 43.5 | 64.9 | 39 | 52 | 52.0 | 76.0 |
| Basel | 44.2 | 67.5 | 42 | 58 | 62.5 | 94.9 |
| St. Gallen | 44.8 | 66.3 | 41 | 55 | 53.8 | 80.4 |
| Bern | 45.7 | 68.2 | 56 | 81 | 76.4 | 128.6 |
| Zurich | 57.0 | 83.9 | 56 | 75 | 76.0 | 102.7 |
| Solothurn | 56.3 | 84.2 | 52 | 75 | 59.1 | 86.6 |
| Schaffhausen | 57.6 | 85.3 | 58 | 82 | 65.1 | 91.7 |
| Appenzell | 58.4 | 90.8 | 56 | 73 | 52.1 | 72.4 |
| Valais | 62.6 | 94.1 | 51 | 80 | 70.6 | 110.0 |
| Lucerne | 65.2 | 96.5 | 81 | 97 | 106.7 | 128.6 |
| Schwyz | 69.1 | 101.2 | 42 | 53 | 94.6 | 117.7 |
| Aargau | 75.0 | 111.6 | 55 | 70 | 79.2 | 110.5 |
| Grisons | 81.6 | 130.4 | 70 | 121 | 111.7 | 236.0 |
| Unterwalden | 90.1 | 132.0 | 43 | 58 | 129.9 | 161.3 |
| Ticino | 98.0 | 147.1 | 95 | 147 | 141.3 | 230.3 |
| Neuchâtel | 115.5 | 174.7 | 72 | 140 | 143.4 | 306.5 |
| Uri | 121.7 | 178.2 | 80 | 107 | 173.8 | 304.8 |
| Jura | 131.2 | 191.3 | 87 | 150 | 128.7 | 254.2 |
| Glarus | 133.8 | 196.0 | 94 | 129 | 143.4 | 233.4 |

[a]Predictions refer to bedrooms, Gammadata as dosimeter type and to the period from 2001 to 2004.

[b]Population weighted and floor corrected measurements.

[c]Measurements, carried out in different type of rooms, situated on all floors except in inhabited basements.

measurements in their home. A model-based indoor radon assessment takes into account the within-municipality variability of geologic and soil features and also building characteristics. This indicates that in a large-scale epidemiological study, where many individual household predictions are needed, a model-based approach considering the individual characteristics of each house is a more reliable method than simply taking a community-level mean of household measurements.

The model-based approach has the further advantage of overcoming the selection bias that results from the direct measurement approach if measurement sites are selected in a nonrepresentative way. The FOPH gives priority to conducting measurements in households in municipalities and buildings with a high radon risk (personal communication). This confirms that households were selected in a nonrepresentative way. Rooms were more likely to be selected for measurements if they were located in high radon risk buildings or in buildings located in high-risk areas. The study results showed that the application of this high-risk sampling strategy resulted in an overestimation of the true residential radon concentration. Taking detached houses as an example, the agreement between model-based and measurement-based exposure assessments was lower for cantons where a high-risk site selection strategy was applied.

The nonrepresentative selection of measurement sites has also been used in other countries, namely in Sweden and in the United States (Cohen, 1991; Swedjemark and Mjönes, 1984). The study from the United States found higher values for urban areas than for suburban areas in the midwest of the United States due to the selection of urban areas in regions with a high radon risk (Cohen, 1991). Due to the selection of high radon risk sites, the Swedish study of Pershagen presents higher averages of measured radon values than a more recent study of radon and lung cancer among people in Sweden who have never smoked (Lagarde et al., 2001; Pershagen et al., 1994). The arithmetic means of measured values are therefore expected to overestimate the true exposure of the population in the area under investigation. Thus, studies that rely on radon exposure assessments based on measurements only and, using a high-risk sampling strategy, should be viewed with caution.

Menzler et al. (2008) took a different approach to overcoming the problem of nonrepresentative selection of measurement sites by considering the population distribution within municipalities and within buildings. A floor correction factor of 0.83 was used (Menzler

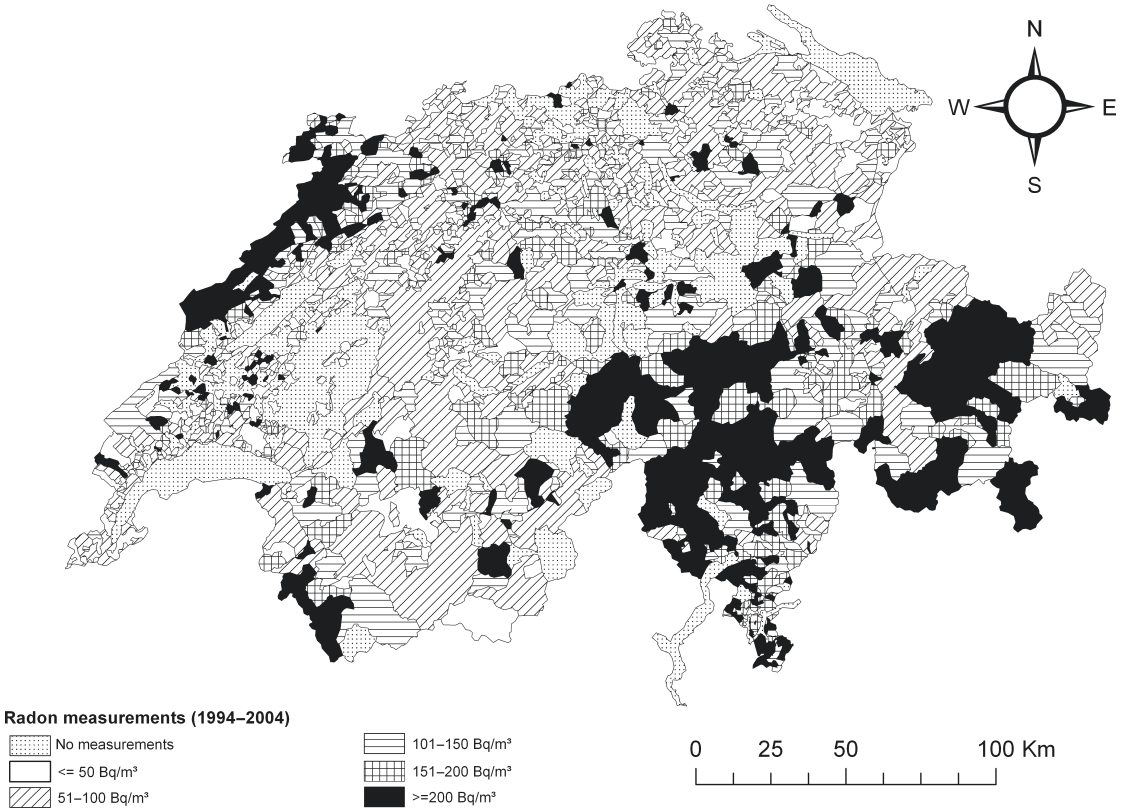


**Fig. 3** Municipality averages (arithmetic means) of radon measurements, carried out between 1994 and 2004, excluding inhabited basements. Digital map of municipalities (2007) was kindly provided by Swiss Federal Statistical Office, GEOSTAT; radon measurement, carried out between 1994 and 2004, was kindly provided by the Swiss Federal Office of Public Health (FOPH)

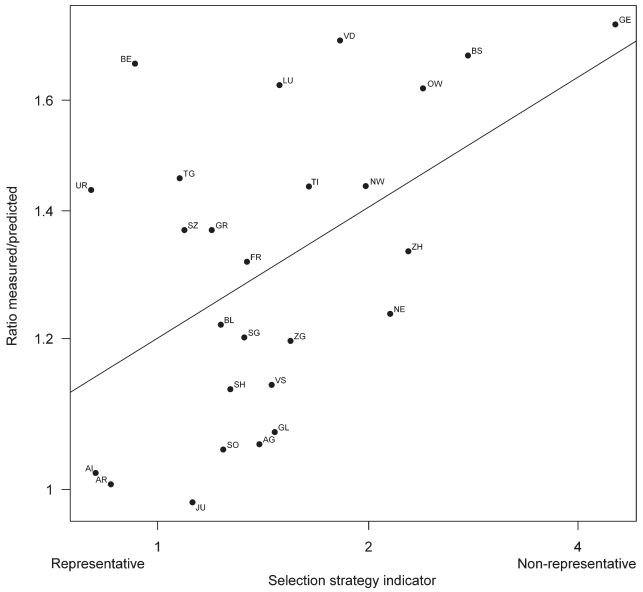


**Fig. 4** Ratio of measurements divided by predictions against the application of different measurement selection strategies, taking the example of detached houses. Because radon levels are known to be higher in detached houses, we calculated as selection strategy indicator the proportion of measured detached houses in a canton divided by the proportion of all detached houses

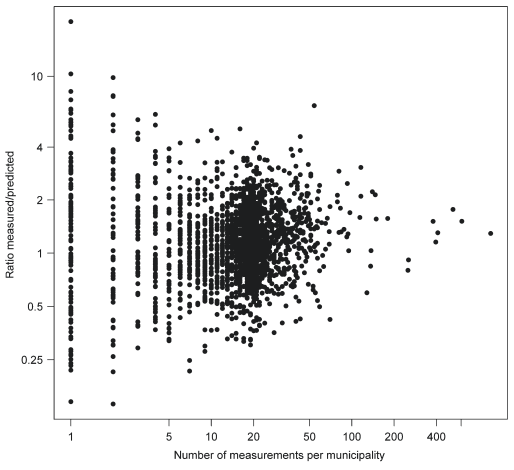


**Fig. 5** Ratio of measurements divided by predictions against the number of measurements per municipality

and Kreienbrock, 2005). This means that for prediction of radon levels on upper floors, ground floor measured radon levels were multiplied by 0.83 for each increase in floor number. In our prediction model, with floor considered as continuous predictor in the dataset, the estimated floor correction model coefficient was 0.86.

This may partly explain why the model-based predictions were on average, 8% higher than the measurement-based predictions.

At the cantonal level, moderate (0.7) Spearman rank correlations were found between model-based and measurement-based predictions, although the differences between the two approaches were large for some cantons. These differences have probably been introduced due to the fact that the model-based predictions considered a broad spectrum of prediction factors, such as the characteristics of each building in Switzerland, whereas the measurement-based approach consisted of just averaging available radon measurements within a municipality. Thus, within-municipality variability of relevant predictors such as soil or geology was not accounted for. Correlation at the municipality level was considerably lower. Theoretically, it is expected that correlation further decreases with the downsizing of the unit of observation. Using direct measurements, the uncertainty of the estimated average exposure for a given area depends on the number of available measurements for that area. The fewer the measurements available, the larger the uncertainty because the measured houses may not be representative of the corresponding area. In contrast, uncertainties in the model-based approach depend on the underlying regression model and not on the number of available measurements per area, which is an advantage for estimating average radon exposure in a specific area in the context of a risk assessment. The errors of the model are expected to cancel out one another with increasing aggregation size, which is not necessarily true for selection and participation bias using a measurement-based approach. As the model-based approach allows the estimation of radon exposure distribution in a given area, it is possible to estimate the percentage of households in each canton, which exceed the reference value of 100 Bq/m$^3$. This is, however, difficult with the measurement-based approach unless a high proportion of houses are measured or the measurement sites have been randomly selected.

Nevertheless, besides the aforementioned advantages, model-based predictions also have some limitations. The model was found to underestimate peak radon exposures. The underestimation of peak values is probably due to missing relevant predictors that were not considered in the prediction model. Data relating to different possible relevant predictors (e.g., daily room ventilation, type of fundament, degree of underpressure in a particular building, sealing between the houses and the ground) do not exist at the national level. An underestimation of peak radon exposures could also have resulted from the application of a linear regression model that assumed a log-normal distribution of the measured radon values. The literature suggests that such a model might be suitable for assessing moderate radon concentration levels, but not for higher values, as the log normality assumption would not be valid for the extreme upper values (Tuia and Kanevski, 2008). Nevertheless, the model is useful for systematically identifying buildings posing a high risk of radon exposure to its occupants, although the critical threshold may be set somewhat lower than the target because the model tends to underestimate the very high radon levels.

Our predictions indicated that the legal action level, as defined by the WHO as the level beyond which modifications to the construction of the houses are necessary, that is, 100 Bq/m$^3$, is frequently exceeded in the Jurassic and the Alpine regions. According to the guidelines of the WHO, the model-based predictions indicated that modifications to the construction of the houses are necessary for almost one-third of all Swiss households. Using an action threshold level of 300 Bq/m$^3$, the model-based predictions indicate that around 1% of households in the Alpine and Jurassic region exceed this. Our model may therefore be used to guide the identification of houses where interventions would be beneficial.

Radon exposure has been found to be associated with lung cancer in adults (Darby et al., 2005; Krewski et al., 2006), as its decay products irradiate the respiratory tract (Axelson et al., 1988). It is the primary cause of lung cancer among people who have never smoked (WHO, 2009). WHO estimates that the risk of lung cancer increases by 20% per 100 Bq/m$^3$ with between 3% and 14% of all lung cancer deaths being related to radon exposure while considering any level of radon exposure having the potential to cause lung cancer (WHO, 2009). In Switzerland, it was calculated that almost 10% of lung cancer deaths are due to indoor radon concentrations at an estimated average of 78 Bq/m$^3$ (Menzler et al., 2008). Although this proportion is slightly higher if with the model-based exposure assessment, both approaches yield similar average population exposure.

In summary, the advantage of the measurement-based approach is that its simplicity is sufficient for assessing exposure distribution in a population, for example, in the context of a health impact assessment. The model-based approach allows the prediction of radon levels at specific sites, which is important in the context of an epidemiological study. Furthermore, the model-based approach is not affected by potential bias if measurement sites are selected preferentially in higher risk radon areas. Uncertainties of the model-based approach depend on the underlying regression model and not on the number of available measurements per community. The model-based approach also allows the estimation of radon exposure in specific subgroups (e.g., age-groups, regions, or building age) and is useful for identifying buildings with a high radon risk in a systematic way.

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#### Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Exposure assessment for the year 2000: household based predictions: all floors: different cantons.

**Table S2.** Comparisons: distribution of households, selected for radon measurements with households from the national census 2000.

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## Article 3: Domestic radon exposure and risk of childhood cancer: a prospective census-based cohort study

This article has been accepted by the Environmental Health Perspectives

# Domestic Radon Exposure and Risk of Childhood Cancer: A Prospective Census-Based Cohort Study

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**Background:** In contrast with established evidence linking high doses of ionizing radiation with childhood cancer, research on low-dose ionizing radiation and childhood cancer has produced inconsistent results.

**Objective:** We investigated the association between domestic radon exposure and childhood cancers, particularly leukemia and central nervous system (CNS) tumors.

**Methods:** We conducted a nationwide census-based cohort study including all children < 16 years of age living in Switzerland on 5 December 2000, the date of the 2000 census. Follow-up lasted until the date of diagnosis, death, emigration, a child's 16th birthday, or 31 December 2008. Domestic radon levels were estimated for each individual home address using a model developed and validated based on approximately 45,000 measurements taken throughout Switzerland. Data were analyzed with Cox proportional hazard models adjusted for child age, child sex, birth order, parents' socioeconomic status, environmental gamma radiation, and period effects.

**Results:** In total, 997 childhood cancer cases were included in the study. Compared with children exposed to a radon concentration below the median (< 77.7 Bq/m$^3$), adjusted hazard ratios for children with exposure ≥ the 90th percentile (≥ 139.9 Bq/m$^3$) were 0.93 (95% CI: 0.74, 1.16) for all cancers, 0.95 (95% CI: 0.63, 1.43) for all leukemias, 0.90 (95% CI: 0.56, 1.43) for acute lymphoblastic leukemia, and 1.05 (95% CI: 0.68, 1.61) for CNS tumors.

**Conclusions:** We did not find evidence that domestic radon exposure is associated with childhood cancer, despite relatively high radon levels in Switzerland.

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## Introduction

Childhood cancer is the second most common cause of death in children (after accidents) in developed countries (Jemal et al. 2010; UK Childhood Cancer Study Investigators 2000). Incidence rates of childhood malignancies increased by approximately 1% per year in Europe between 1970 and 1999 (Kaatsch et al. 2006; McKinney 2005; Steliarova-Foucher et al. 2004), and this increase did not slow down in the first 5 years after 2000 (Pritchard-Jones et al. 2006). In the United States, the incidence of childhood malignancies increased by approximately 0.5% per year between 1992 and 2007 (Kohler et al. 2011).

Low-dose ionizing radiation is hypothesized to cause childhood cancer. Radon is a decay product of uranium, a naturally occurring element in granitic and metamorphic rocks (Ball et al. 1991; Gillmore et al. 2005; Gunderson 1992). Radon emanates from soil and concentrates inside buildings. Domestic radon is a major natural source of ionizing radiation exposure. Worldwide, radon is estimated to contribute to roughly half of the average annual ionizing radiation dose (Charles 2001). In Switzerland, this figure was estimated to be 60% (Federal Office of Public Health 2011).

Because of the high fat content of red bone marrow, it has been suggested that radon gas doses delivered to this organ may be high enough to damage stem cells (Tong et al. 2012) and increase the risk of childhood leukemia (Richardson 2008). The relationship between radon exposure and childhood leukemia has been addressed in various case–control studies (Cartwright et al. 2002; Kaletsch et al. 1999; Kendall et al. 2013; Lubin et al. 1998; Maged et al. 2000; Raaschou-Nielsen et al. 2008; Steinbuch et al. 1999; Stjernfeldt et al. 1987) and ecological studies (Alexander et al. 1990; Butland et al. 1990; Collman et al. 1991; Evrard et al. 2005, 2006; Foreman et al. 1994; Gilman and Knox 1998; Henshaw et al. 1990; Lucie 1990; Muirhead et al. 1991; Richardson et al. 1995; Thorne et al. 1996a, 1996b). Most of the ecological studies reported an association between childhood leukemia and estimated domestic radon exposure. However, because these were population-level analyses, control for individual-level confounders was not possible. Results of case–control studies have been inconsistent (Laurier et al. 2001; Tong et al. 2012), with some studies reporting an association (Maged et al. 2000; Raaschou-Nielsen et al. 2008) and others not (Cartwright et al. 2002; Kaletsch et al. 1999; Kendall et al. 2013; Lubin et al. 1998; Steinbuch et al. 1999; Stjernfeldt et al. 1987). A recent analysis of a Danish case–control study reported evidence that air pollution from road traffic might enhance the association between radon and childhood leukemia (Bräuner et al. 2012). The authors speculated

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that attachment of radon decay products to traffic exhaust particles may have been responsible for this observation.

For central nervous system (CNS) tumors, which are almost all found in the brain (McKinney 2005), only a few ecological (Collman et al. 1991; Henshaw et al. 1990; Thorne et al. 1996b) and case–control studies (Cartwright et al. 2002; Kaletsch et al. 1999; Kendall et al. 2013; Raaschou-Nielsen et al. 2008) have been performed, also showing inconsistent results. Ecological studies have suggested an association between domestic radon concentration and CNS tumors (Collman et al. 1991; Henshaw et al. 1990; Thorne et al. 1996b). Two large case–control studies performed in Denmark (Raaschou-Nielsen et al. 2008) and the United Kingdom (Kendall et al. 2013) reported no evidence of an association. In contrast, a German study (Kaletsch et al. 1999) reported elevated risks of CNS tumors associated with radon exposures > 70 Bq/m$^3$. However, the association was based on six exposed cases only.

In view of these conflicting results, we conducted a prospective census-based cohort study to investigate whether domestic radon exposure is associated with childhood cancers, particularly leukemia and CNS tumors. In addition, we evaluated whether exposure to traffic-related air pollution [i.e., nitrogen dioxide ($NO_2$)] might modify associations.

## Methods

***Databases.*** We used data from the Swiss National Cohort (SNC 2011), which is described in detail elsewhere (Bopp et al. 2009; Spoerri et al. 2010). Briefly, the SNC is a nationwide longitudinal research platform that links census data collected in 1990 and 2000 with birth records, mortality records, and emigration data. It includes data on all persons living in Switzerland at the time of each census, including individual- and household-level data (e.g., information on child sex, birth order within each household, and the socioeconomic status of adults based on highest education and socioprofessional category), as well as building information. Participation in the census was compulsory, and the coverage for 2000 was estimated to be 98.6% (Renaud 2004). For this study we included all children between 0 and 15 years of age living in Switzerland on 5 December 2000.

Incident cancer cases in the SNC were identified by probabilistic record linkage with the Swiss Childhood Cancer Registry (SCCR) based on birth date, sex, and residential geocodes. The SCCR is a longitudinal national database founded in 1976 by the Swiss Pediatric Oncology Group (SPOG) (Michel et al. 2008). This registry contains baseline information and long-term follow-up information on cancer patients < 21 years of age (Kuehni et al. 2012). Registration of children diagnosed with cancer before 16 years of age is estimated to be at least 95% (Kuehni et al. 2012).

Of 1,127 cases identified in the SCCR, 2 were excluded because their cancer was diagnosed after they emigrated from Switzerland and 117 were excluded because they could not be successfully linked with records in the SNC (Figure 1). The remaining 1,008 were linked to the SNC cohort consisting of 1,332,944 children. Finally, 45,590 (including 11 cases and 45,579 noncases) were excluded from our analysis because their exact place of residence was uncertain (e.g., because they were living in emergency accommodations, mobile or provisional dwellings, or buildings that could not be geocoded), leaving 997 cases and a total cohort of 1,287,354 children for the main analysis. In addition, we conducted a sensitivity analysis that also included 51 of the 117 cases who could not be linked to the SNC, but had address information from the 2000 census (1,048 cases in a total cohort of 1,287,405 children). This study is based on register data, and informed consent was not required. The SNC was approved by the ethics committees in Bern (205/06) and Zurich (13/06) and by the Federal Data Protection Office.

***Exposure assessment.*** We estimated indoor radon exposure at baseline (5 December 2000) for each child's home address using a nationwide radon prediction model (Hauri

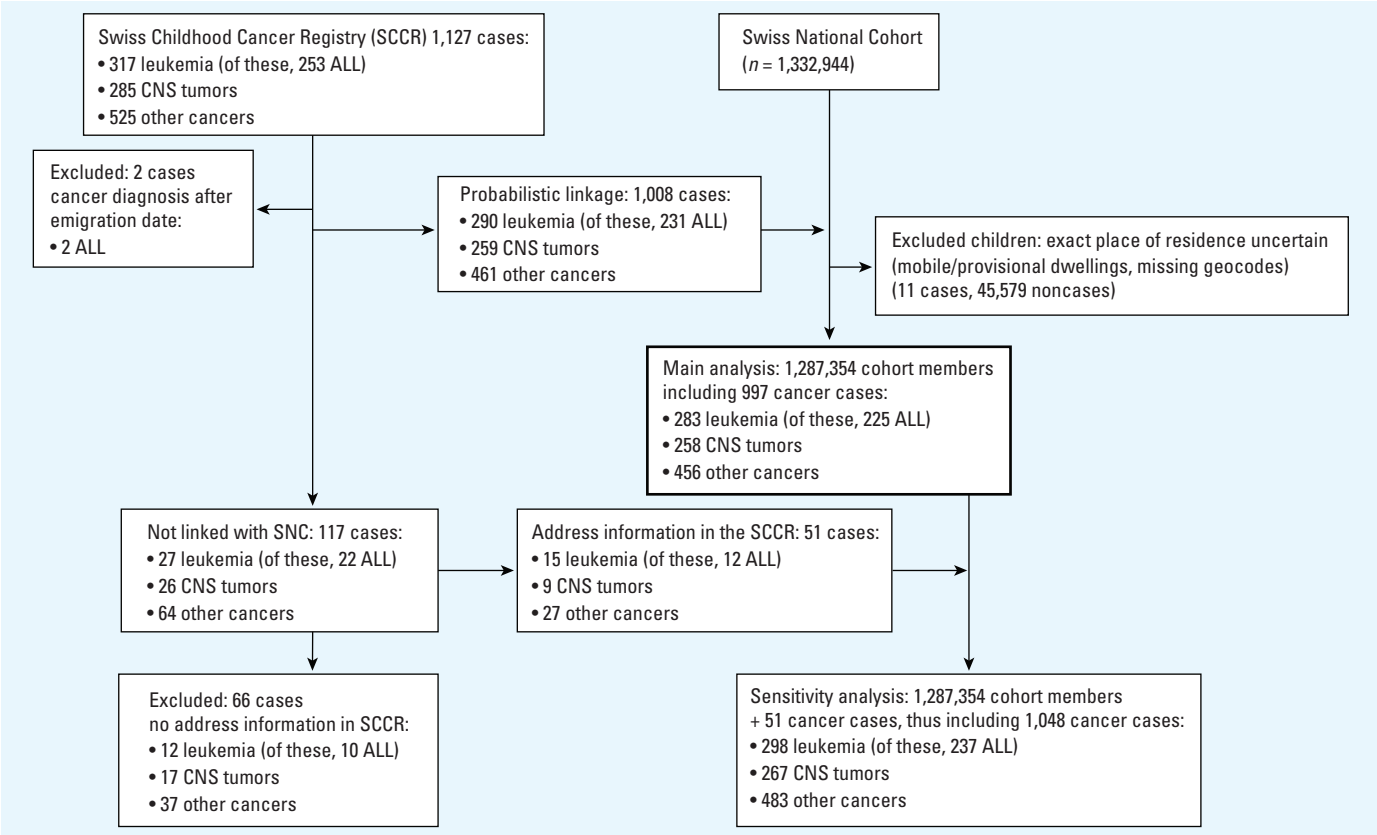


**Figure 1.** Overview on the study population obtained from linking the Swiss Childhood Cancer registry to the Swiss National Cohort. ALL, acute lymphoblastic leukemia.

et al. 2012, 2013). The prediction model is a log-linear regression model that was developed based on 35,706 measurements, carried out in Switzerland between 1994 and 2004. Relevant predictors in the model were tectonic units, building age, building type, soil texture, degree of urbanization, and floor level (Hauri et al. 2012). The adjusted $R^2$ was 20%. The model was validated using an independent data set of 8,925 radon measurements that were not used to develop the model. Spearman rank correlations between predicted and measured radon values were 0.45 (95% CI: 0.44, 0.46) for the development data set and 0.44 (95% CI: 0.42, 0.46) for the validation data set. Using a cut-off at the 90th percentile, areas under the ROC (receiver operating characteristic) curve were 0.73 (95% CI: 0.72, 0.74) for the development set and 0.72 (95% CI: 0.71, 0.74) for the validation set. Sensitivity was 0.31 for the development and 0.29 for the validation data set, and specificity was 0.92 for both data sets.

We evaluated potential confounders identified from the literature on environmental risk factors for childhood cancer and leukemia (McNally and Parker 2006; Tong et al. 2012). The following factors were considered: distance to major roads, railways, and electric power lines; particulate matter air pollution ($PM_{10}$; ≤ 10 μm in aerodynamic diameter), $NO_2$, and ambient benzene concentrations; exposure to radiofrequency electromagnetic fields from broadcast transmitters; and potential exposure to agricultural pesticides based on distance to the nearest orchard, vineyard, or golf course. In addition, we considered distance to the nearest pediatric cancer center because it may be associated with the completeness of childhood cancer registration, which may be better in areas with a pediatric cancer center than in the rest of Switzerland, and with the spatial distribution of radon. We estimated exposures to potential confounders from digital maps, using ArcGIS (ESRI, Redlands, CA, USA). We extracted data on background gamma radiation exposure from Swiss radiation maps (Rybach et al. 2002) with a grid cell resolution of 2 km. We obtained digital maps of power lines with a resolution of 1:25,000, from the Federal Inspectorate for Heavy Current Installations. Distances to major roads were obtained using digital maps on the traffic network with a resolution of 1:25,000 (VECTOR25-maps), published by the Federal Office of Topography (swisstopo) (2010). Data distances to orchards, vineyards, and golf courses (used to estimate exposure to agricultural pesticides) were derived from Swiss land use statistics for 1997 (Arealstatistik Schweiz), published by the Swiss Federal Statistical Office (Neuchâtel, Switzerland; http://www.bfs.admin.ch) with a grid cell resolution of 100 m × 100 m. Pediatric cancer centers were manually geocoded using the fixed point data service of the Federal Office of Topography (2010). We extracted modeled benzene levels for the year 2005 from a digital map with a grid cell resolution of 400 m, published by the Swiss Agency for the Environment, Forests and Landscape (Heldstab et al. 2004) and extracted $PM_{10}$ and $NO_2$ exposure levels from 2005 from digital maps with a grid cell resolution of 100 m, published by the Federal Office of the Environment (Heldstab et al. 2011). Exposure to analogous, digital radio, and digital TV broadcast transmitters was modeled for the year 2000 for residences within 10 km of a transmitter. Exposure to short-wave radio and medium-wave radio was modeled for the year 1997 for residences within 20 km of these transmitters. These models were developed by the Federal Office of Communications (Biel, Switzerland; http://www.bakom.admin.ch).

We used exposure to $PM_{10}$, $NO_2$, and benzene ambient concentrations as linear variables. The other factors were used categorically with predefined as exposure corridors for distance to major roads [> 400 m to highways or > 200 m to main roads (class 1), 100–400 m to highways or 50–200 m to main roads, 40–100 m to highways or 20–50 m to main roads, < 40 m to highways or < 20 m to main roads], to high voltage power lines (including railways) (< 50 m, 50–200 m, 200–600 m, > 600 m), to agricultural pesticides [distance to the nearest orchards (> 200 m, 100–200 m, 50–100 m, < 50 m)], to vineyards (> 500 m, 250–500 m, 100–250 m, < 100 m), to golf courses (> 3,000 m, 1,500–3,000 m, 750–1,500 m, < 750 m), and to the nearest pediatric center (> 30 km, 15–30 km, 5–15 km, < 5 km). Exposure categories for the radio frequency–electromagnetic frequency exposure were used, with a cut-off at 0.05 and 0.2 V/m to differentiate among low, medium, and high exposures. Residences outside the model area were considered in the lowest exposure category.

***Statistical analysis.*** We analyzed data using Cox proportional hazard models with age as the underlying time scale. Time at risk began on 5 December 2005 (the date of the census) and ended on the date of diagnosis, death, emigration, the child's 16th birthday, or 31 December 2008, whichever occurred first. We categorized exposure using *a priori* cut points at the 50th and 90th percentiles. In addition, we conducted linear exposure–response analyses of radon concentration modeled as simple continuous predictor. Hazard ratios (HRs) are expressed per 100 $Bq/m^3$ increase in radon exposure. All models were adjusted for child sex, birth order within each household (linearly), socioeconomic status of the parents using the parents' highest education (low, medium, high, no information) and their job position (low, medium, high, unemployed/retired/housewife/volunteer work, no information), as well as total background gamma radiation exposure from cosmic, terrestrial, and artificial ground radiation from the Chernobyl event [by categorizing at the 50th, 103 nSV/h (nanoSieverts per hour); and 90th percentiles, 133 nSV/h], and period effects (by dichotomizing follow-up time into two 4-year blocks). We added potential confounders to models one at a time and used a change-in-estimation criterion of 10% to select covariates for the final model (Greenland 1989). None of the potential confounders met this criterion; therefore our final models included child sex, birth order, socioeconomic status, background gamma radiation exposure, and period only. We confirmed the proportional hazard assumption using Nelson–Aalen survival functions and statistical tests based on Schoenfeld residuals and by examining variation in associations between covariates and the outcomes varied over time (data not shown).

***Subgroup and sensitivity analyses.*** Because a recent case–control study (Bräuner et al. 2012) suggested an interaction between domestic radon exposure and $NO_x$ (nitrogen oxides) from traffic exhaust, we stratified our analysis at the median $NO_2$ concentration in our cohort (21.6 $\mu g/m^3$). Further, we evaluated possible effect modification by sex because the risk of cancer is higher for boys than girls (Michel et al. 2008). We also conducted separate analyses for preschool children (< 5 years of age) and schoolchildren (5–15 years of age) because young children may be more vulnerable to exposure from ionizing radiation than older children (Little et al. 2010). In addition, for children 5–15 years of age, we evaluated the effect of exposure misclassification due to residential mobility (Warner et al. 1995) by conducting separate analyses of children who did or did not move residence between 1995 and 2000 based on information available in the SNC.

We also carried out a separate regional analysis for cantons that lie at least partly in the Alpine region (Grisons, Appenzell, Bern, Glarus, Lucerne, Unterwalden, Schwyz, St. Gallen, Ticino, Uri, Valais, Vaud) where the highest radon concentrations were found.

Finally, we performed a sensitivity analysis that included 51 cases who could not be linked to the SNC but had information in the SCCR on place of residence at the time of the 2000 census. Because we did not have information on the floor they lived on, building age, or building type for these children, we estimated their radon exposures assuming that they lived on the first floor of apartment buildings built between 1946 and 1970, consistent with average values for all children based on the 2000 census. These models were adjusted for sex, environmental gamma radiation, and period effects, but not for socioeconomic status of the parents or birth order.

## Results

In the SNC database 1,332,944 children were identified who were between 0–15 years of age on the date of the 2000 census. Of these, 45,590 were excluded because their exact place of residence was unclear (Figure 1). In total, we analyzed data from 1,287,354 children, accumulating 7,627,646 person-years during the study period. From the 1,127 cancer cases identified in the SCCR who were diagnosed between 2000 and 2008, 997 could be linked to the SNC database. Of these, 283 were diagnosed with leukemia [including 225 with acute lymphoblastic leukemia (ALL)] and 258 with a CNS tumor.

The estimated median radon concentration for all cohort members was 77.7 Bq/m$^3$, and the 90th percentile was 139.9 Bq/m$^3$ (see Supplemental Material, Table S1). The arithmetic mean radon concentration was 85.7 Bq/m$^3$ (range, 6.9–337.2 Bq/m$^3$) for childhood cancer cases and 85.9 Bq/m$^3$ (range, 0.7–490.1 Bq/m$^3$) for the rest of the study population. Arithmetic mean radon concentrations were lowest (84.0 Bq/m$^3$) for ALL cases and highest for CNS tumor cases (88.9 Bq/m$^3$).

Results of the main analysis are shown in Table 1 and Figure 2. Compared with children exposed to a radon concentration below the median, HRs for children with exposure ≥ 90th percentile (≥ 139.9 Bq/m$^3$) were 0.93 (95% CI: 0.74, 1.16) for all cancers, 0.95 (95% CI: 0.63, 1.43) for all leukemias, 0.90 (95% CI: 0.56, 1.43) for ALL, and 1.05 (95% CI: 0.68, 1.61) for CNS tumors. Age-adjusted risk estimates were very similar to the fully adjusted results (Table 1). There was no evidence of linear exposure–response associations for any of the outcomes (Table 1). Including 51 additional cancer cases who had address information but could not be linked to the SNC had little influence on effect estimates (see Supplemental Material, Table S2). The subgroup analyses also did not indicate evidence of effect modification by age, sex, or moving status (see Supplemental Material, Table S3). Restricting the analyses to Alpine cantons, where radon levels are highest, also did not indicate an association between domestic radon concentration and childhood cancer (data not shown). Analyses stratified according to low or high $NO_2$ exposure (< 21.6 or ≥ 21.6 μg/m$^3$, respectively) did not provide evidence of an interaction between $NO_2$ and domestic radon concentration for any of the outcomes (Table 2).

## Discussion

Our census-based cohort study did not indicate an association between domestic radon concentration and childhood cancer. The results were consistent across various sensitivity and subgroup analyses, and for different types of cancer.

To our knowledge, other cohort studies on domestic radon concentration and childhood cancers have not been published. The main strength of the present study is its nationwide coverage, which substantially reduces the likelihood of selection bias. Exposure assessment was based on a comprehensive prediction model that was developed and validated using > 40,000 measurements taken throughout Switzerland between 1994 and 2004. Previous case–control studies have reported participation < 55%, and exposure measurements were often limited to subsets of study participants (Cartwright et al. 2002; Kaletsch et al. 1999; Lubin et al. 1998; Maged et al. 2000; Steinbuch et al. 1999; Stjernfeldt et al. 1987). In contrast with ecological studies, we had information on a number of potential individual-level confounders (Laurier et al. 2001; Tong et al. 2012), although adjusting for these variables did not materially affect hazard ratios, suggesting little or no confounding by these factors although we cannot completely exclude residual confounding due to misclassification in the confounder variables. This is consistent with the current knowledge on childhood cancer etiology: There is evidence of increased risks among children with a genetic predisposition and among those exposed to high doses of ionizing radiation (e.g., applied for cancer treatment), but little evidence of environmental risk factors (Belson et al. 2007; Eden 2010; McKinney 2005; Pollack

**Table 1.** Age-adjusted and fully adjusted hazard ratios (HRs) for childhood cancer and residential radon exposure.

| Cancer type | Radon exposure | No. of cancer cases | Person-years | Age-adjusted HR (95% CI) | Fully adjusted HR (95% CI)[a] |
|---|---|---|---|---|---|
| All cancers | < 77.7 Bq/m$^3$ | 525 | 3,838,101 | Reference | Reference |
| | 77.7–139.9 Bq/m$^3$ | 373 | 3,034,923 | 0.90 (0.79, 1.03) | 0.89 (0.78, 1.02) |
| | ≥ 139.9 Bq/m$^3$ | 99 | 754,623 | 0.96 (0.78, 1.19) | 0.93 (0.74, 1.16) |
| | per 100 Bq/m$^3$ | 997 | | 1.01 (0.87, 1.16) | 0.99 (0.85, 1.14) |
| All leukemias | < 77.7 Bq/m$^3$ | 149 | 3,838,101 | Reference | Reference |
| | 77.7–139.9 Bq/m$^3$ | 104 | 3,034,923 | 0.90 (0.70, 1.15) | 0.86 (0.67, 1.11) |
| | ≥ 139.9 Bq/m$^3$ | 30 | 754,623 | 1.04 (0.70, 1.54) | 0.95 (0.63, 1.43) |
| | per 100 Bq/m$^3$ | 283 | | 0.97 (0.74, 1.27) | 0.90 (0.68, 1.19) |
| ALL | < 77.7 Bq/m$^3$ | 121 | 3,838,101 | Reference | Reference |
| | 77.7–139.9 Bq/m$^3$ | 81 | 3,034,923 | 0.86 (0.65, 1.15) | 0.83 (0.63, 1.11) |
| | ≥ 139.9 Bq/m$^3$ | 23 | 754,623 | 0.99 (0.63, 1.55) | 0.90 (0.56, 1.43) |
| | per 100 Bq/m$^3$ | 225 | | 0.94 (0.69, 1.28) | 0.86 (0.63, 1.19) |
| CNS tumors | < 77.7 Bq/m$^3$ | 132 | 3,838,101 | Reference | Reference |
| | 77.7–139.9 Bq/m$^3$ | 99 | 3,034,923 | 0.95 (0.73, 1.23) | 0.95 (0.73, 1.23) |
| | ≥ 139.9 Bq/m$^3$ | 27 | 754,623 | 1.05 (0.69, 1.59) | 1.05 (0.68, 1.61) |
| | per 100 Bq/m$^3$ | 258 | | 1.18 (0.91, 1.54) | 1.19 (0.91, 1.57) |

For the categorical analysis, radon exposure levels were categorized at 50th and 90th percentile of the exposure distribution.

[a]In addition to using age as the underlying time scale, adjusted for child sex, birth order, socioeconomic status of the parents, environmental gamma radiation, and period effects.

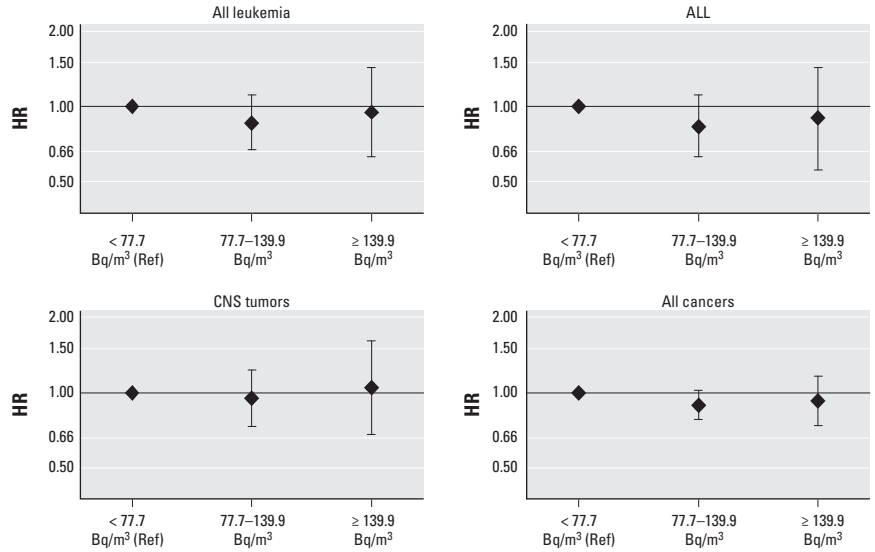


**Figure 2.** HRs and 95% CIs for associations between domestic radon concentrations at baseline and all leukemias, ALL, CNS tumors, and all cancers diagnosed among Swiss children during 2000–2008. Ref, reference. Models are adjusted for child sex, birth order, socioeconomic status of the parents, environmental gamma radiation, and period effects, in addition to using age as the underlying time scale.

and Jakacki 2011). Only two previous case–control studies had similar methodological features to the present study—large sample size, consideration of confounding, radon exposure estimation based on prediction models, and a small likelihood of selection bias due to the use of population-based controls identified from registries without requiring consent for participation (Kendall et al. 2013; Raaschou-Nielsen et al. 2008). In contrast with our study, a Danish study reported that domestic radon exposure was associated with ALL (rate ratio = 1.56; 95% CI: 1.05, 2.30 per 1,000 Bq/m$^3$–years) based on 860 cases diagnosed between 1968 and 1994, and 1,720 registry-based controls (Raaschou-Nielsen et al. 2008). However, no association was reported between radon concentrations and CNS tumors (rate ratio = 0.92; 95% CI: 0.69, 1.22 per 1,000 Bq/m$^3$–years based on 922 CNS tumor cases). In a British study, the estimated relative risk for leukemia per 1,000 Bq/m$^3$–years increase in cumulative radon exposure was 1.12 (95% CI: 0.88, 1.43) based on 9,058 cases and 11,912 controls, and the corresponding estimate for CNS tumors was 1.15 (95% CI: 0.88, 1.50) based on 6,585 cases and 8,997 controls (Kendall et al. 2013).

Recently, associations between radon and nonrespiratory cancers also have been investigated in adults. Consistent associations were not observed between nonrespiratory cancer mortality and ecologic measures of residential radon levels in the large prospective American Cancer Society cohort, which includes > 1 million participants (Turner et al. 2012). For example, the HR for leukemia mortality was 0.93 (95% CI: 0.82, 1.05) per 100-Bq/m$^3$ increase in mean county-level residential radon concentrations. These findings are consistent with a collaborative analysis of 11 studies of miners that indicated that leukemia mortality was not associated with radon exposure (Darby et al. 1995). Wheeler et al. (2012) reported evidence of an association between radon levels and skin cancer in an ecological study conducted in southwest England during 2000–2004 (Wheeler et al. 2012). The authors speculated that radon and its decay products are attracted to water molecules, and that the resulting aerosols could adhere to the skin via electrostatic attraction. Such a mechanism was also proposed in a subsequent analysis of the Danish case–control study that reported evidence that air pollution ($NO_x$) from road traffic strengthened associations between radon and childhood leukemia (Bräuner et al. 2012). Our study results, however, do not support such an interaction.

Our study also has limitations, and given the fact that we did not observe an association the main concern may be that we have missed a true association due to lack of power, or exposure misclassification. Our study included fewer cases than did the two large register-based case–control studies from Denmark (Raaschou-Nielsen et al. 2008) and Great Britain (Kendall et al. 2013). However, estimated exposure levels were larger in our Swiss study population on average (arithmetic mean radon concentration, 86 Bq/m$^3$; range, 0.7–490.1 Bq/m$^3$) than in the Danish (arithmetic mean concentration, 48 Bq/m$^3$; range, 4 to 254 Bq/m$^3$) and British studies (arithmetic mean radon in the control group, 21.3 Bq/m$^3$; range, 1.2–692 Bq/m$^3$). Little et al. (2010) pointed out that in epidemiological studies of cancer and ionizing radiation, statistical power is influenced much more by differences in mean dose than by the number of cases. Thus, in terms of statistical power, the large differences in exposure levels of our study population may at least partly compensate for the smaller number of cases. Regarding exposure misclassification, we deal in our study mainly with a Berkson-type error because we used a prediction model (Heid et al. 2004; Raaschou-Nielsen et al. 2008; Steenland et al. 2000). Unlike errors of individual measurements, this type of error does not bias estimates of associations towards unity, but instead reduces statistical power resulting in wider confidence intervals (Armstrong 1998; Steenland et al. 2000). Although non-Berkson error may have been introduced in the exposure assessment if people changed their place of residence, associations based on cohort members who did not relocate during the 5 years before 2000 were similar to estimates for the cohort as whole, suggesting that exposure misclassification did not substantially bias our findings.

The observed lack of an association between domestic radon exposure and childhood leukemia or CNS tumors is consistent with expectations, given low estimated doses of exposure to domestic radon for red bone marrow and the CNS. For a 1-year-old child, an annual radon concentration of 100 Bq/m$^3$ [i.e., the radon concentration where remedial actions are recommended according to the World Health Organization (2009)] corresponds to an equivalent dose to the lung of 19.6 mSv per year (Kendall and Smith 2005). Organ-specific doses for red bone marrow (0.43 mSv) or the brain (0.19 mSv) are much smaller (Kendall and Smith 2002, 2005). Comparable values were estimated for 10-year-old children (lung: 21.1 mSv; red bone marrow: 0.52 mSv; and brain: 0.14 mSv) (Kendall and Smith 2005). These dose estimations support our observed results and suggest that doses from domestic radon levels to organs other than the lung are too weak to noticeably increase cancer risks.

**Table 2.** Age-adjusted and fully adjusted hazard ratios (HRs) for childhood cancer and radon exposure within strata of $NO_2$ concentration.

| Cancer type and $NO_2$ exposure all cancers | Radon exposure | No. of cases | No. of person-years | HR (95% CI)[a] |
|---|---|---|---|---|
| All cancers | | | | |
| $NO_2$ < 21.6 µg/m$^3$ | < 77.7 Bq/m$^3$ | 220 | 1,690,638 | Reference |
| | 77.7–139.9 Bq/m$^3$ | 185 | 1,635,275 | 0.85 (0.70, 1.03) |
| | ≥ 139.9 Bq/m$^3$ | 70 | 465,612 | 1.08 (0.82, 1.43) |
| $NO_2$ ≥ 21.6 µg/m$^3$ | < 77.7 Bq/m$^3$ | 305 | 2,147,462 | Reference |
| | 77.7–139.9 Bq/m$^3$ | 188 | 1,399,648 | 0.96 (0.80, 1.15) |
| | ≥ 139.9 Bq/m$^3$ | 29 | 289,011 | 0.74 (0.50, 1.11) |
| All leukemias | | | | |
| $NO_2$ < 21.6 µg/m$^3$ | < 77.7 Bq/m$^3$ | 63 | 1,690,638 | Reference |
| | 77.7–139.9 Bq/m$^3$ | 44 | 1,635,275 | 0.69 (0.47, 1.02) |
| | ≥ 139.9 Bq/m$^3$ | 22 | 465,612 | 1.08 (0.65, 1.80) |
| $NO_2$ ≥ 21.6 µg/m$^3$ | < 77.7 Bq/m$^3$ | 86 | 2,147,462 | Reference |
| | 77.7–139.9 Bq/m$^3$ | 60 | 1,399,648 | 1.07 (0.77, 1.49) |
| | ≥ 139.9 Bq/m$^3$ | 8 | 289,011 | 0.77 (0.37, 1.62) |
| ALL | | | | |
| $NO_2$ < 21.6 µg/m$^3$ | < 77.7 Bq/m$^3$ | 54 | 1,690,638 | Reference |
| | 77.7–139.9 Bq/m$^3$ | 34 | 1,635,275 | 0.62 (0.40, 0.95) |
| | ≥ 139.9 Bq/m$^3$ | 17 | 465,612 | 0.92 (0.52, 1.64) |
| $NO_2$ ≥ 21.6 µg/m$^3$ | < 77.7 Bq/m$^3$ | 67 | 2,147,462 | Reference |
| | 77.7–139.9 Bq/m$^3$ | 47 | 1,399,648 | 1.08 (0.75, 1.58) |
| | ≥ 139.9 Bq/m$^3$ | 6 | 289,011 | 0.78 (0.33, 1.82) |
| CNS tumors | | | | |
| $NO_2$ < 21.6 µg/m$^3$ | < 77.7 Bq/m$^3$ | 60 | 1,690,638 | Reference |
| | 77.7–139.9 Bq/m$^3$ | 49 | 1,635,275 | 0.86 (0.59, 1.26) |
| | ≥ 139.9 Bq/m$^3$ | 18 | 465,612 | 1.14 (0.66, 1.96) |
| $NO_2$ ≥ 21.6 µg/m$^3$ | < 77.7 Bq/m$^3$ | 72 | 2,147,462 | Reference |
| | 77.7–139.9 Bq/m$^3$ | 50 | 1,399,648 | 1.05 (0.73, 1.52) |
| | ≥ 139.9 Bq/m$^3$ | 9 | 289,011 | 0.91 (0.44, 1.89) |

For the categorical analysis, radon exposure levels categorized at 50th and 90th percentile of the exposure distribution. $NO_2$ exposure levels categorized at 50th percentile of the exposure distribution.
[a]In addition to using age as the underlying time scale, adjusted for child sex, birth order, socioeconomic status of the parents, environmental gamma radiation, and period effects.

## Conclusions

In summary, we did not find evidence that domestic radon exposure is associated with childhood leukemia or CNS tumors, despite relative high radon levels in Switzerland.

### Correction

The values for age-adjusted hazard ratios (HRs) (95% CIs) for all leukemias in Table 1 and for HR (95% CI) for all leukemias ($NO_2$ < 21.6 μg/m$^3$, ≥ 139.9 Bq/m$^3$) in Table 2 were incorrect in the manuscript originally published online. They have been corrected here.

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# Supplemental Material

# Domestic Radon Exposure and Risk of Childhood Cancer: A Prospective Census-Based Cohort Study

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Supplemental Material, Table S1: Characteristics of all cohort members.

| Characteristics | | Study participants No. (%) | Cancer cases [No. (%)] | | | | Radon exposure of all cohort members (Bq/m³) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | All cancers | Leukemia | ALL | CNS | arithmetic mean | median | 90th percentile |
| All participants | | 1,287,354 (100) | 997 (100) | 283 (28.4) | 225 (22.6) | 258 (25.9) | 85.9 | 77.7 | 139.9 |
| Gender | boys | 658,960 (51.2) | 561 (56.3) | 168 (59.4) | 133 (59.1) | 138 (53.5) | 85.9 | 77.7 | 139.9 |
| | girls | 628,394 (48.8) | 436 (43.7) | 115 (40.6) | 92 (40.9) | 120 (46.5) | 85.9 | 77.7 | 139.7 |
| Age | < 5 years | 373,017 (29.0) | 170 (39.0) | 72 (25.4) | 62 (27.6) | 42 (16.3) | 84.3 | 76.1 | 137.6 |
| | 5-15 years | 914,337 (71.0) | 609 (61.0) | 211 (74.6) | 163 (72.4) | 216 (83.7) | 86.6 | 78.5 | 140.2 |
| Parents' socio-economic status | | | | | | | | | |
| Education | low | 165,126 (13.4) | 106 (11.1) | 23 (8.3) | 20 (9.1) | 27 (10.8) | 80.4 | 72.0 | 134.9 |
| | medium | 627,851 (50.8) | 476 (49.6) | 153 (55.4) | 116 (52.5) | 117 (45.446.6) | 88.5 | 79.9 | 143.8 |
| | high | 443,770 (35.9) | 377 (39.3) | 100 (36.2) | 85 (38.5) | 107 (42.6) | 85.4 | 78.2 | 136.0 |
| | no information[a] | 50,607 | 38 | 7 | 4 | 7 | 74.6 | 67.0 | 122.8 |
| Job position | low | 131,441 (11.1) | 89 (9.7) | 20 (7.5) | 16 (7.6) | 19 (8.1) | 83.6 | 74.6 | 140.2 |
| | medium | 487,787 (41.2) | 393 (43.0) | 120 (44.9) | 98 (46.5) | 107 (45.7) | 86.2 | 78.2 | 138.5 |
| | high | 233,786 (19.8) | 193 (21.1) | 52 (19.5) | 42 (19.9) | 51 (21.8) | 84.6 | 77.4 | 134.0 |
| | unemployed/retired/ housewife/volunteer work | 330,609 (27.9) | 239 (26.2) | 75 (28.1) | 55 (26.1) | 57 (24.4) | 88.8 | 80.0 | 144.6 |
| | no information[a] | 103,731 | 83 | 16 | 14 | 24 | 81.4 | 73.3 | 133.3 |

Age at time of census 2000 was considered for indicating the number of all cohort members and cancer cases and when reporting radon concentrations (arithmetic mean, median, 90th percentile. Age at time of diagnosis was considered when indicating the number of cancer cases.

[a]Education, job position: observations with missing data were included within a separate category in the analyses.

Supplemental Material, Table S2: Consideration of additional 51 cancer cases not linked to the SNC but with addresses available at the date of census 2000 (December 5 2000).

| Cancer type | Radon exposure | No. cancer cases | No. of person-years | Crude HR (95% CI) | Adjusted HR (95% CI) |
|---|---|---|---|---|---|
| All cancers (n=1,048) | <77.7 Bq/m³ | 558 | 3,838,207 | Reference | Reference |
| | 77.7-139.9 Bq/m³ | 384 | 3,034,959 | 0.90 (0.79, 1.03) | 0.89 (0.78, 1.02) |
| | ≥ 139.9 Bq/m³ | 106 | 754,648 | 0.96 (0.78, 1.19) | 0.93 (0.74, 1.16) |
| All leukaemias (n=298) | <77.7 Bq/m³ | 158 | 3,838,207 | Reference | Reference |
| | 77.7-139.9 Bq/m³ | 109 | 3,034,959 | 0.89 (0.69, 1.13) | 0.88 (0.69, 1.12) |
| | ≥ 139.9 Bq/m³ | 31 | 754,648 | 1.02 (0.69, 1.49) | 0.97 (0.65, 1.45) |
| ALL (n=236) | <77.7 Bq/m³ | 127 | 3,838,207 | Reference | Reference |
| | 77.7-139.9 Bq/m³ | 86 | 3,034,959 | 0.86 (0.65, 1.15) | 0.86 (0.65, 1.13) |
| | ≥ 139.9 Bq/m³ | 24 | 754,648 | 0.99 (0.63, 1.55) | 0.92 (0.58, 1.47) |
| CNS tumors (n=267) | <77.7 Bq/m³ | 135 | 3,838,207 | Reference | Reference |
| | 77.7-139.9 Bq/m³ | 103 | 3,034,959 | 0.96 (0.75, 1.25) | 0.96 (0.74, 1.24) |
| | ≥ 139.9 Bq/m³ | 29 | 754,648 | 1.10 (0.74, 1.65) | 1.09 (0.72, 1.65) |

Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval; CNS tumors, central nervous system tumors; HR, hazard ratio

fully adjusted models**:** in addition to using age as the underlying time scale, adjusted for gender, the environmental gamma radiation and period effects. Radon exposure levels categorized at $50^{th}$ and $90^{th}$ percentile of the exposure distribution.

Supplemental Material, Table S3: Subgroup analyses of the association between domestic radon levels and various childhood cancer types by gender, age-group and history of moving.

| Cancer type | Radon exposure | Gender | | | | Age | | | | Moving status between 1995 and 2000: 5-15 years old | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | boys | | girls | | < 5 years | | 5-15 years | | not moved | | moved | |
| | | No. cases | adj. HR (95% CI) | No. cases | adj. HR (95% CI) | No. cases | adj. HR (95% CI) | No. cases | adj. HR (95% CI) | No. cases | adj. HR (95% CI) | No. cases | adj. HR (95% CI) |
| All cancers | <77.7 Bq/m³ | 285 | Reference | 240 | Reference | 87 | Reference | 438 | Reference | 192 | Reference | 110 | Reference |
| | 77.7-139.9 Bq/m³ | 218 | 0.95 (0.80, 1.14) | 155 | 0.82 (0.67, 1.00) | 65 | 0.99 (0.72, 1.38) | 308 | 0.87 (0.75, 1.01) | 144 | 0.83 (0.67, 1.03) | 72 | 0.85 (0.63, 1.15) |
| | ≥ 139.9 Bq/m³ | 58 | 1.00 (0.74, 1.34) | 41 | 0.85 (0.60, 1.20) | 18 | 1.09 (0.64, 1.85) | 81 | 0.90 (0.70, 1.15) | 44 | 0.87 (0.62, 1.23) | 16 | 0.85 (0.50, 1.46) |
| All leukaemias | <77.7 Bq/m³ | 84 | Reference | 65 | Reference | 38 | Reference | 111 | Reference | 40 | Reference | 25 | Reference |
| | 77.7-139.9 Bq/m³ | 67 | 0.99 (0.71, 1.36) | 37 | 0.70 (0.47, 1.05) | 28 | 0.95 (0.58, 1.56) | 76 | 0.82 (0.61, 1.10) | 31 | 0.83 (0.52, 1.34) | 20 | 1.00 (0.55, 1.80) |
| | ≥ 139.9 Bq/m³ | 17 | 0.95 (0.55, 1.63) | 13 | 0.97 (0.52, 1.80) | 6 | 0.77 (0.32, 1.90) | 24 | 1.00 (0.63, 1.58) | 12 | 1.02 (0.52, 2.03) | 5 | 1.22 (0.46, 3.24) |
| ALL | <77.7 Bq/m³ | 66 | Reference | 55 | Reference | 33 | Reference | 88 | Reference | 29 | Reference | 20 | Reference |
| | 77.7-139.9 Bq/m³ | 53 | 0.99 (0.69, 1.43) | 28 | 0.64 (0.40, 1.01) | 23 | 0.93 (0.54, 1.59) | 58 | 0.80 (0.57, 1.11) | 21 | 0.76 (0.43, 1.35) | 15 | 0.93 (0.48, 1.82) |
| | ≥ 139.9 Bq/m³ | 14 | 0.94 (0.51, 1.72) | 9 | 0.85 (0.41, 1.75) | 6 | 0.92 (0.37, 2.28) | 17 | 0.88 (0.51, 1.51) | 6 | 0.66 (0.26, 1.68) | 5 | 1.43 (0.52, 3.95) |
| CNS tumors | <77.7 Bq/m³ | 70 | Reference | 62 | Reference | 19 | Reference | 113 | Reference | 50 | Reference | 27 | Reference |
| | 77.7-139.9 Bq/m³ | 51 | 0.89 (0.62, 1.29) | 48 | 1.01 (0.69, 1.48) | 19 | 1.35 (0.71, 2.58) | 80 | 0.88 (0.66, 1.18) | 36 | 0.80 (0.52, 1.23) | 16 | 0.75 (0.40, 1.39) |
| | ≥ 139.9 Bq/m³ | 17 | 1.19 (0.68, 2.08) | 10 | 0.87 (0.44, 1.73) | 4 | 1.37 (0.46, 4.11) | 23 | 0.99 (0.62, 1.59) | 12 | 0.96 (0.50, 1.85) | 3 | 0.54 (0.16, 1.88) |

Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval; CNS tumors, central nervous system tumors; HR, hazard ratio. Fully adjusted models**:** in addition to using age as the underlying time scale, adjusted for gender, birth order, socio-economic status of the parents, the environmental gamma radiation and period effects. Radon exposure levels categorized at $50^{th}$ and $90^{th}$ percentile of the exposure distribution.

# 4 Exposure to background gamma radiation and childhood cancer

For the second aim of this dissertation, i.e. the assessment on background gamma radiation and childhood cancer, the same number of study participants and cancer cases as for the analyses on domestic radon exposure (Article 3) and the time-to-event analyses on broadcast transmitters (Article 4) were considered. That is 1,332,944 children were identified in the SNC, aged less than 16 years at the date of census 2000. Of these 45,590 children were excluded as their exact place of residence was unclear. In total data from 1,287,354 children were analysed accumulating 7,627,646 person-years during the study period. 997 childhood cancer cases were included in the study. Of these, 283 cases were diagnosed with leukaemia, (225 ALL) and 258 with a CNS tumour.

The estimated median dose rate from terrestrial, cosmic and artificial gamma radiation for all study participants was 103 nSv/h and the 90$^{th}$ percentile was 133 nSv/h. Arithmetic mean of the estimated dose rates was 109 nSv/h (range: 55 - 247 nSv/h) for childhood cancer cases and 108 nSv/h (range: 55 – 383 nSv/h) for the rest of the study population. Arithmetic mean of the estimated dose rates was slightly lower (109 nSv/h) for CNS tumour cases than for leukaemia and ALL cases (110 nSv/h). When considering doses to the population from the different sources, the largest contribution is from terrestrial radiation (arithmetic mean: 54 nSv/h), followed by cosmic radiation (46 nSv/h). Contribution of doses from artificial radiation to the population is far less important (arithmetic mean: 8 nSv/h).

When considering doses from background gamma radiation within different regions in Switzerland, they were estimated to be highest in the Alpine regions (Figure 6) as the intensity of cosmic radiation increases with altitude and due to the presence of crystalline massifs in the Alps. They were estimated to be lowest for the Central Plateau due to its lower altitude and due to the presence of sedimentary rocks.

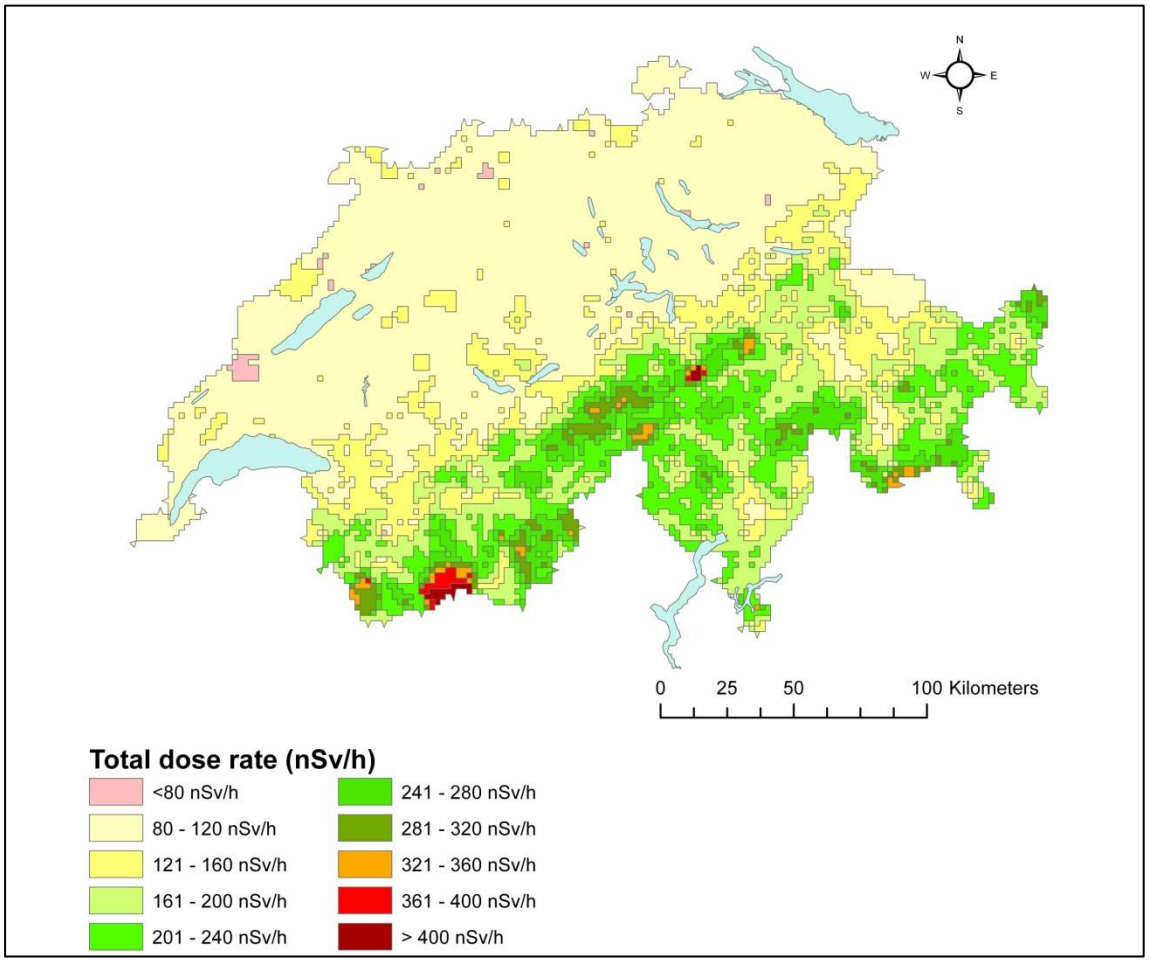


**Figure 6: Total dose rate map (nSv/h) of Switzerland, based on Rybach et al. (2002). Doses depicted on this map do not consider the population distribution. This becomes evident, as doses rates above 400 nSv/h were measured in non-inhabited areas. Digital map of the Swiss boundary (2001) was kindly provided by the Swiss Federal Statistical Office, GEOSTAT**

Results from the main analyses are shown in Table 3 and Figure 7. The main analyses did not show associations between background gamma radiation and childhood cancer. Compared with children exposed to a gamma radiation dose below the median (< 103 nSv/h), hazard ratios (HR) for children with exposure ≥ 90th percentile (≥133 nSv/h) were 1.09 (95% confidence interval (CI): 0.87, 1.36) for all cancers, 1.13 (95% CI: 0.75, 1.69) for all leukaemias, 1.20 (95% CI: 0.76, 1.87) for ALL and 1.09 (95% CI: 0.70, 1.68) for CNS tumours. There was no evidence of a linear exposure-response association and the results also did not indicate any effect modification by age (Table 3).

When restricting the analysis to children who lived at the same address between 1995 and 2000, elevated hazard ratios for all leukaemias and for ALL were noted (Table 4).

For the most exposed leukaemia cases (including ALL), significant hazard ratios were estimated. Compared with children exposed to a gamma radiation dose below the median (< 103 nSv/h), hazard ratios (HR) for children with exposure ≥ 90th percentile (≥ 133 nSv/h) was 2.02 (95%-CI: 1.05, 3.87) for all leukaemias and 2.59 (95%-CI: 1.22, 5.47) for ALL. A dose response trend is visible for both all leukaemias and ALL which becomes also obvious from the linear dose-response analysis (Table 4). In contrast, no elevated hazard ratios were noted for these health outcomes when restricting the analyses to children who moved between 1995 and 2000. On the other hand, elevated hazard ratios for CNS tumours in children who moved during that time period where found, and the result was significant for the medium exposure category (Table 4).

**Table 3: Fully adjusted hazard ratios (HR) for childhood cancer by exposure categories and per 100nSv/h**

| | Age 0-16 years | | | Age 0-4 years | | | Age 5-15 years | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Cases** | **HR[a]** | **95% CI** | **Cases** | **HR[a]** | **95% CI** | **Cases** | **HR[a]** | **95% CI** |
| all cancers | | | | | | | | | |
| <103 nSv/h | 501 | 1 | Referent | 84 | 1 | Referent | 417 | 1 | Referent |
| 104-133 nSv/h | 396 | 1.17 | 1.02, 1.33 | 66 | 1.20 | 0.87, 1.66 | 330 | 1.16 | 1.01, 1.35 |
| >133 nSv/h | 100 | 1.09 | 0.87, 1.36 | 20 | 1.27 | 0.76, 2.11 | 80 | 1.05 | 0.82, 1.35 |
| per 100 nSv/h | | 1.19 | 0.91, 1.55 | | 1.32 | 0.71, 2.45 | | 1.17 | 0.87, 1.56 |
| leukaemia | | | | | | | | | |
| <103 nSv/h | 142 | 1 | Referent | 38 | 1 | Referent | 104 | 1 | Referent |
| 104-133 nSv/h | 111 | 1.16 | 0.90, 1.49 | 25 | 1.01 | 0.60, 1.68 | 86 | 1.23 | 0.92, 1.63 |
| >133 nSv/h | 30 | 1.13 | 0.75, 1.69 | 9 | 1.34 | 0.63, 2.84 | 21 | 1.07 | 0.66, 1.73 |
| per 100 nSv/h | | 1.26 | 0.78, 2.04 | | 1.45 | 0.57, 3.69 | | 1.23 | 0.70, 2.14 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ALL | | | | | | | | | |
| <103 nSv/h | 114 | 1 | Referent | 34 | 1 | Referent | 80 | 1 | Referent |
| 104-133 nSv/h | 86 | 1.11 | 0.84, 1.47 | 21 | 0.92 | 0.53, 1.59 | 65 | 1.19 | 0.86, 1.66 |
| >133 nSv/h | 25 | 1.20 | 0.76, 1.87 | 7 | 1.09 | 0.47, 2.53 | 18 | 1.24 | 0.73, 2.11 |
| per 100 nSv/h | | 1.37 | 0.81, 2.33 | | 1.26 | 0.45, 3.53 | | 1.41 | 0.76, 2.62 |
| CNS | | | | | | | | | |
| <103 nSv/h | 128 | 1 | Referent | 23 | 1 | Referent | 105 | 1 | Referent |
| 104-133 nSv/h | 104 | 1.21 | 0.93, 1.57 | 15 | 1.04 | 0.54, 2.00 | 89 | 1.25 | 0.94, 1.66 |
| >133 nSv/h | 26 | 1.09 | 0.70, 1.68 | 4 | 0.94 | 0.31, 2.82 | 22 | 1.12 | 0.70, 1.80 |
| per 100 nSv/h | | 1.09 | 0.64, 1.84 | | 0.45 | 0.09, 2.28 | | 1.24 | 0.71, 2.16 |

[a] in addition to using age as the underlying time scale**,** adjusted for gender, birth order, socio-economic status of the parents, domestic radon exposure and period effects. For the categorical analysis, gamma exposure levels were categorised at 50$^{th}$ and 90$^{th}$ percentile of the exposure distribution

**Table 4: Subgroup analysis of the association between ionizing gamma radiation and childhood cancer by history of moving**

| | moving status: not moved (aged 5-15 years) | | | moving status: moved (aged 5-15 years) | | |
|---|---|---|---|---|---|---|
| | **Cases** | **HR[a]** | **95% CI** | **Cases** | **HR[a]** | **95% CI** |
| all cancers | | | | | | |
| ≤103 nSv/h | 182 | 1 | Referent | 96 | 1 | Referent |
| 104-133 nSv/h | 149 | 1.21 | 0.97, 1.50 | 87 | 1.32 | 0.99, 1.77 |
| >133 nSv/h | 49 | 1.34 | 0.97, 1.86 | 15 | 1.03 | 0.59, 1.79 |
| per 100 nSv/h | | 1.49 | 1.02, 2.17 | | 1.10 | 0.57, 2.14 |
| leukaemia | | | | | | |
| ≤103 nSv/h | 33 | 1 | Referent | 30 | 1 | Referent |
| 104-133 nSv/h | 36 | 1.63 | 1.01, 2.61 | 17 | 0.83 | 0.46, 1.52 |
| >133 nSv/h | 14 | 2.02 | 1.05, 3.87 | 3 | 0.61 | 0.18, 2.05 |
| per 100 nSv/h | | 2.02 | 1.00, 4.10 | | 0.67 | 0.16, 2.83 |

| | | | | | | |
|---|---|---|---|---|---|---|
| ALL | | | | | | |
| ≤103 nSv/h | 23 | 1 | Referent | 23 | 1 | Referent |
| 104-133 nSv/h | 22 | 1.40 | 0.78, 2.52 | 14 | 0.89 | 0.46, 1.73 |
| >133 nSv/h | 11 | 2.59 | 1.22, 5.47 | 3 | 0.75 | 0.22, 2.59 |
| per 100 nSv/h | | 2.51 | 1.09, 5.79 | | 1.01 | 0.25, 4.17 |
| CNS | | | | | | |
| ≤103 nSv/h | 51 | 1 | Referent | 16 | 1 | Referent |
| 104-133 nSv/h | 36 | 1.03 | 0.67, 1.58 | 25 | 2.27 | 1.21, 4.26 |
| >133 nSv/h | 11 | 1.05 | 0.54, 2.07 | 5 | 2.21 | 0.79, 6.18 |
| per 100 nSv/h | | 1.22 | 0.56, 2.67 | | 2.38 | 0.74, 7.60 |

[a] in addition to using age as the underlying time scale**,** adjusted for gender, birth order, socio-economic status of the parents, domestic radon exposure and period effects. For the categorical analysis, gamma exposure levels are categorised at $50^{th}$ and $90^{th}$ percentile of the exposure distribution

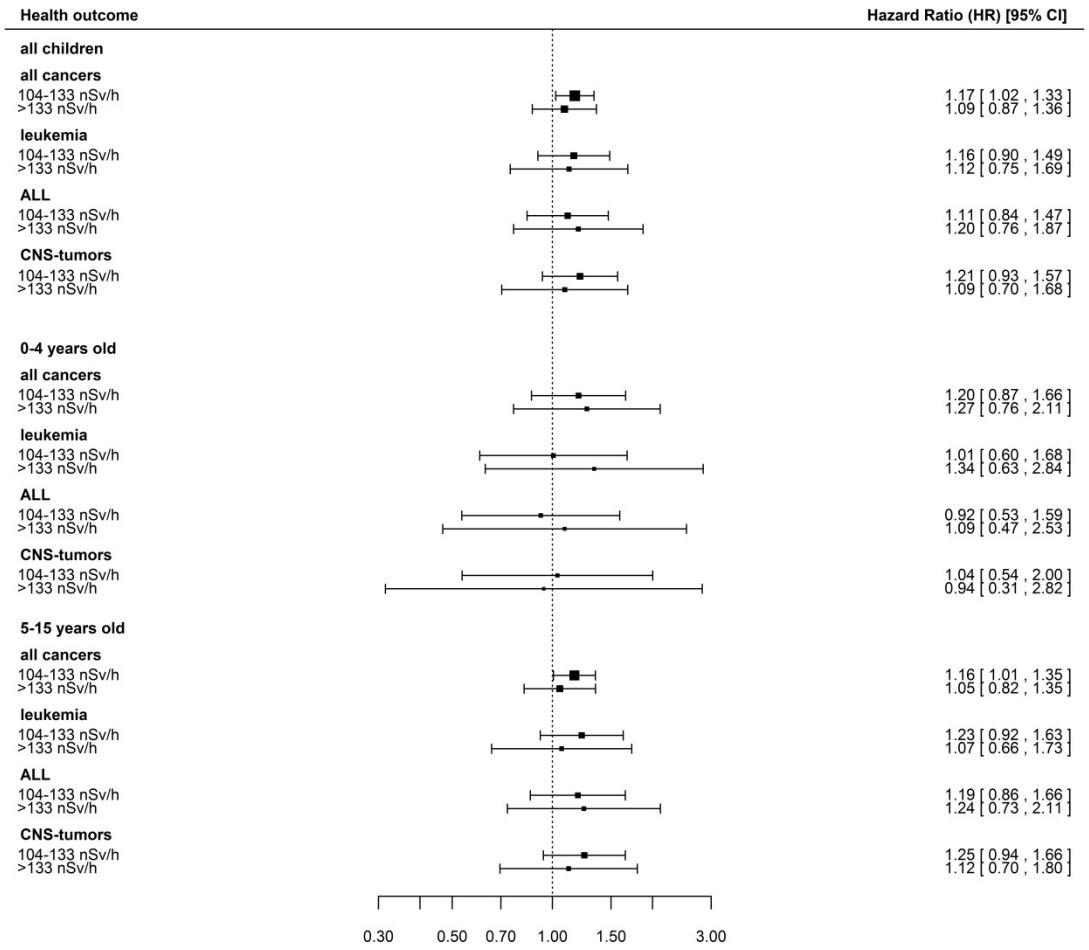


**Figure 7: HRs from Cox regression with adjustment for age, gender, birth order within each household, domestic radon exposure, socio-economic status of the parents and period effects**

# 5 Exposure to radio-frequency electromagnetic fields from broadcast transmitters and childhood cancer

## Article 4: Exposure to radiofrequency electromagnetic fields from broadcast transmitters and risk of childhood cancer: a census-based cohort study

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# *Exposure to radiofrequency electromagnetic fields from broadcast transmitters and risk of childhood cancer: a census-based cohort study*

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## ABSTRACT

This study consisted in investigating the association between RF-EMF exposure and childhood cancer in a census based cohort study in Switzerland. We conducted a Cox regression including children aged less than 16 years and living in Switzerland on December 5th 2000. Follow-up lasted until 31 December 2008. Second, all children, aged less than 16 years and resident in Switzerland for some time between January 1985 and December 2008 were included in a Poisson regression analysis. Modeled RF-EMF exposure from broadcast transmitters was considered.

We included 997 childhood cancer cases in the time-to-event analysis and 4,246 cancer cases in the Poisson analysis. In the time-to-event analysis, hazard ratios (HR) for the highest exposure category (≥ 0.2 V/m) compared to the reference group (<0.05 V/m) were 1.03 (95% CI 0.74, 1.43) for all cancers, 0.55 (95%-CI: 0.26, 1.19) for leukemia, 0.61 (95%-CI: 0.27, 1.41) for ALL and 1.71 (95% CI 0.99, 2.94) for CNS tumors. Results of the Poisson analysis were similar for all types of cancer and leukemia but found no indication for a CNS tumor risk (1.03, 95%-CI: 0.73, 1.46). This large census based cohort study indicates no association between RF-EMF from broadcasting and childhood leukemia. Results for CNS tumors were less consistent.


**Keywords:** Lymphoblastic Leukemia, Acute, Childhood; neoplasms; Central nervous system tumor; electromagnetic fields; radio waves

Radio-frequency electromagnetic fields (RF-EMF) from broadcast transmitters (radio and TV transmitters) have been hypothesized to cause childhood cancer, although a biological mechanism has not been identified for low exposure levels (1, 2). The IARC (International Agency for Research on Cancer) classified RF-EMF as "possible carcinogenic (2B)" based on positive associations between glioma and acoustic neuroma and exposure to RF-EMF from wireless phones (3). With respect to studies that addressed the possible association between cancer and environmental exposure to RF-EMF from fixed site transmitters the IARC Working Group found the available evidence insufficient to draw conclusion.

Radiofrequency electromagnetic fields from broadcast transmitters are spaced far apart, but, individually, cover large areas and therefore generate relatively high fields at ground level. Provided landscape factors (local topography, morphology, soil conductivity, vegetation) are accounted for, epidemiological exposure assessment is less vulnerable to exposure misclassification than for other environmental RF-EMF sources such as mobile phone base stations, which display a much higher spatial variation (4, 5).

Most studies on this topic so far focused on childhood leukemia, using an ecological study design (6-11) or case-control study design (12-14). A few studies on childhood leukemia included also central nervous system tumors (CNS tumors) (12, 13) or primary tumors of the brain (6, 8, 11-13). In most ecological studies leukemia incidence was increased in the proximity of broadcast transmitters, reaching statistical significance in some (7, 8, 10, 11) but not all studies (6, 9, 15). However, lack of individual exposure data and lack for confounding adjustment is a severe limitation for interpretation.

Only recently, two large case-control studies with individual exposure assessment based on modeling were published. A Korean study (12, 13) involved 1,928 childhood leukemia cases diagnosed between 1993 and 1999 and an equal number of matched hospital-based controls.

Distance and RF-EMF exposure from 31 amplitude-modulated (AM) radio transmitters were available. Within 2 km of the transmitters a relative risk of 2.15 (95% confidence interval (CI): 1.00–4.67) for all types of leukemia was observed compared to children living more than 20km away from a transmitter. But risk was significantly reduced (odds ratio (OR): 0.66, 95% CI: 0.44-0.99) for children living between 2 and 4 km from a transmitter. No association was observed between childhood leukemia risk and the average predicted field strengths.

The other large case–control study was conducted in German municipalities in the vicinity of 16 AM radio and 8 frequency-modulated (FM) broadcast transmitters (14). It included 1,959 cases diagnosed between 1984 and 2003 and at age 0-14 years. It included three population based controls per case, matched on age, sex and transmitter area. This study found no indication for an association between RF-EMF and childhood leukemia. Risk was also not increased for the first exposure decade before mobile communication was introduced on a large scale and where broadcasting was the dominant environmental RF-EMF source. These two case-control studies are superior to previously published ecological studies due to their sample size and individual exposure modeling. However, lack of individual confounding data is a limitation for both studies. Childhood central nervous system CNS tumors are almost always found in the brain (16, 17) and have been speculated to be associated with EMF exposure (16, 18). However, among the different studies on RF-EMF exposure and CNS tumors, only the Korean case-control study (12, 13) used individually modeled exposure data. In this study no association between RF-EMF exposure and childhood CNS tumors was found.

The aim of this study was to investigate within a prospective census-based cohort design the association between RF-EMF exposure from broadcast transmitters and childhood cancer, in particular leukemia and CNS tumors. The objective was to consider individually modeled exposure data and considering potential relevant confounding factors.

## MATERIALS AND METHODS

### Study population

The study was based on data from the Swiss Childhood Cancer Registry (SCCR) and the Swiss National Cohort (SNC). The SCCR includes cancer patients aged less than 21 years at diagnosis. For those aged less than 16 years at diagnosis, at least 95% of incidence cases are registered (19). The SNC, a database with data on all Swiss buildings, households and persons, is a longitudinal research platform linking census data from 1990 and 2000 with each other and with birth records, mortality and emigration data (20, 21). It was compulsory to participate in the census and the coverage for the census 2000 was estimated to be 98.6% (22). For this study we excluded children if their exact place of residence was unclear (i.e. when living in emergency accommodations, mobile or provisional dwellings, buildings with no geo-codes).

We used two strategies to analyze the data: a time-to-event analysis and a aggregated Poisson resident cohort analysis.

#### *Time-to-event analysis.*

For the time-to-event analysis, we included children aged between 0 and 15 years and living in Switzerland at the date of census 2000 (December 5 2000). Time at risk was set to begin at census and lasted until the date of diagnosis, death, emigration, the child's 16th birthday or 31 December, 2008, whichever occurred first. Incident cancer cases in the SNC were identified by means of a probabilistic linkage with the SCCR using information on date of birth, gender, place of residence, place of birth and parent's dates of birth if available. The resulting dataset contained diagnosis-date of cancer cases and information on potential confounders for all study participants: gender, birth order within each household, socio-economic status of the

parents (highest education, socio-professional category) and geospatial data for the place of residence at the date of census.

***Aggregated resident cohort analysis.***

We included in the resident cohort all children, aged less than 16 years and resident in Switzerland for some time between January 1985 and December 2008. Person-time at risk began with the entrance of the person into the cohort, i.e. living in Switzerland in 1985, birth or immigrating to Switzerland between 1985 and 2008. Follow-up period lasted until 2008. For this analysis, no linkage between SCCR and SNC data was necessary. Diagnosed cases were identified from the SCCR. Person years at risk were aggregated by exposure categories for calendar year, gender and one year age strata and estimated by inter-/extrapolation from the SNC data. Thus, it was possible to assess RF-EMF exposure in non-census years as complete as for census years. Details are provided in Spycher et al., 2011 (23).

**Exposure assessment**

For this study we considered all analogous TV-transmitters (very high frequency (VHF) - and ultra high frequency (UHF) band), digital Radio (terrestrial digital audio broadcasting (TDAB), VHF band) and digital TV (digital terrestrial video broadcasting (DVBT), UHF band) (TDAB/analogous TV, i.e. high-band VHF: frequency range: 174 MHz - 230 MHz, analogous TV/digital TV, i.e. UHF band: frequency range: 470-862 MHz) in Switzerland with an output power of >100kW (11 transmitters) as well as transmitter with an output power between 10 and 100 kW if >30,000 persons lived within a circle of 5 km radius (11 transmitters). RF-EMF from these transmitters was modeled by the Federal Office of Communications for an area with a radius of 10 km around each transmitter for the years 1990 and 2000. For the latter date also digital radio was considered. For the aforementioned

area field-strength calculations the CHIRplus_BC software from LS Telcom (XX) and the IRT2D model was applied (24, 25).

RF-EMF from all Swiss short and medium-wave radio transmitters with an output power >1 kW (9 transmitters) were modeled within a distance of 20km of each transmitter for the years 1993 and 1997 using the ICS-Telecom software from ATDI (26) based on Fresnel Deygout method (27). The antenna height, the transmission duration, horizontal and vertical direction of the emissions and the local topography were considered. For overlapping calculated areas the exposure levels of all transmitters was summed up. Year-to-year changes of the emissions from transmitters were in general relatively low until 2008 when analog terrestrial broadcasting and the last medium-wave transmitter (Beromünster) were turned off, except one short-wave transmitter (Schwarzenburg) which was turned off in 1998.

In the time-to-event analysis RF-EMF exposure to radio and TV-transmitters at baseline was assessed for each study participant at the place of residence using the modeled RF-EMF from 2000 and 1997, respectively. In the aggregated resident cohort analysis place of residency at the date of diagnosis was used for the exposure assignment. For children diagnosed before 1995 exposure assessment was based on the models of 1990 and 1993. Thereafter RF-EMF exposure was assessed using the modeled RF-EMF from 2000 and 1997 respectively.

Geospatial data on potential confounders were extracted from digital maps, using ArcGIS based on the place of residence. Data on background gamma radiation were available from the Swiss radiation maps (28) with a grid cell resolution of 2km. Digital maps with power lines with a resolution of 1:25,000 were provided by the Federal Inspectorate for Heavy Current Installations. We extracted distances to the traffic network in 2000 from digital maps on the traffic network with a resolution of 1:25,000 (VECTOR25-maps), published by the Federal Office of Topography (swisstopo). Data on distances to the next orchards, vineyards and golf

courses for the exposure estimation to agricultural pesticides were obtained from the Swiss land use statistics (Arealstatistik Schweiz) of the year 1997, published by the Swiss Federal Statistical Office (BFS) and with a grid cell resolution of 100m. We geo-coded the location of the pediatric cancer centers manually, using the fix point data service (FPDS) of the Federal Office of Topography (29). Data on ambient benzene exposure were available from a digital map with a grid cell resolution of 400m, published by the Swiss Agency for the Environment, Forests and Landscape (SAEFL) (30). Data on PM10 and NO2 exposure were available from digital maps with a grid cell resolution of 100m, published by the Federal Office for the Environment (31). Residential radon exposure was estimated from a nation-wide radon prediction model, based on 44,631 measurements, carried out all over Switzerland between 1994 and 2004 (32).

**Statistical analysis**

For the time-to-event and the aggregated resident cohort analysis the same exposure categories for the RF-EMF exposure were used with a cut-off at 0.05 and 0.2 V/m to differentiate between low, medium and high exposure. Rationales for using categorical exposure data for the primary analyses were uncertainties in the modeled high exposure values and the right-skewed data distribution. All study participants living in an area not covered by the modeling were included in the reference category. We considered RF-EMF exposure from the transmitters together and also separately evaluated VHF- and UHF-transmitters and medium and short wave transmitters. For short and medium wave transmitters, the exposure variable was dichotomized at 0.05 V/m due to the lower levels.

In addition to categorical exposure classification, we also carried out a linear dose-response modeling in the time-to-event analysis using exposure to the broadcast transmitters as

continuous predictor and expressing the hazard ratio per 0.1 V/m increase in exposure. For these analyses exposure levels outside the modeled area were set to 0.001 V/m.

For the time-to-event analysis, Cox proportional hazard regression models were applied using age as the underlying time scale. Time at risk was set to at the date of the census (5$^{th}$ December 2000). Period effects were considered by splitting the follow-up time into a first and a second 4-year block. The basic models were always adjusted for gender. Furthermore, we decided *a priori* to adjust for exposure to benzene since it is an established risk factor for leukemia in adults (33), for natural background ionizing gamma radiation based on the results of a recent large case-control study (34) and for distance to the next high voltage power line, since the IARC evaluated extremely low-frequency magnetic fields (ELF-MF) as possibly carcinogenic, based studies on childhood leukaemia (35). The relevance of additional potential confounding factors was tested in the time-to-event analysis by including one confounder at a time in the model and applying a change-in-estimation criterion of 10% (36). Confounding adjustment was done linearly for birth order within each household, background ionizing gamma radiation, PM10, NO2 and benzene ambient exposure. The other factors were used categorically whereas distances to major roads (>400m to highways or more than 200m to main roads (class 1), 100-400m to highways or 50-200m to main roads, 40-100m to highways or 20-50m to main roads, <40m to highways or <20m to main roads), high voltage power lines (including railways) (<50m, 50-200m, 200-600m, >600m), exposure to agricultural pesticides (distance to the nearest orchards (>200m to orchards, 100-200m, 50-100m, <50m), vineyards (>500m, 250-500m, 100-250m, <100m) or golf courses (> 3,000 m, 1,500-3,000m, 750-1,500m, <750m)) and to the next pediatric center (>30km, 15-30km, 5-15 km, <5 km) were defined as exposure corridors. For domestic radon exposure, we used a categorized exposure variable with a priori set cut-off points at the 50$^{th}$ and 90$^{th}$ percentile (77.7 Bq/m³ and 139.9 Bq/m³ respectively). For the socio-economic status of the adults, we

considered their highest education (low, medium, high, no information) and their job position (low, medium, high, unemployed/retired/housewife/volunteer work, no information). We tested the proportional hazard assumption using the Nelson-Aalen survival functions, by statistical tests based on Schoenfeld residuals and by testing if the effects of covariates vary over time.

Robustness of the time-to-event analysis results was evaluated in two sensitivity analyses: First, we restricted an analysis to children, who were living within the modeled exposure area of the radio and TV transmitters, i.e. within a distance of 10km of the VHF- and UHF-transmitters and within a distance of 20km of the short and medium wave transmitters. Second, the cancer cases identified in the SCCR who could not be linked to the SNC but who's place of residence was available from the SCCR at the time of census 2000 (51 of a total of 1127 cases) (**Figure 1)** were considered in another sensitivity analysis.

For the aggregated analysis, we conducted a Poisson regression analysis. The Poisson regression models were adjusted for gender, age and calendar year. A separate analysis was conducted for the period before 1995 and after 1995. Before 1995, mobile and cordless communication applications were rare and broadcasting was the main environmental RF-EMF exposure source, whereas later, exposure misclassification is expected to be higher and exposure from broadcasting to be less relevant because their relative contribution has become less (5, 37). While exposure to RF-EMF was dominated by broadcast transmitters in the 1990, they were found to account for 11.7% of the total RF-EMF exposure between 2007 and 2008 (37).

The aggregated and the time-to-event analyses were also stratified by age. Separate analysis for pre-school children (i.e. children under the age of five years) and for school children (aged between 5 and 15 years) were conducted.

## RESULTS

For the time-to-event analysis, 1,332,944 children were identified in the SNC database aged between 0 and 15 years at the date of census. Of these, 45,590 children with unclear place of residence were excluded from the analysis (**Figure 1**). In total, 1,287,354 children, accumulating 7,627,646 person-years during the study period were considered for the analysis. We identified 1,127 cancer cases in the SCCR who were diagnosed between 2000 and 2008. Of these, 997could be linked to the SNC database (**Figure 1**). Of these, 283 cases were diagnosed with leukemia, (225 acute lymphoblastic leukemia (ALL)) and 258 with a CNS tumor.

Of the 1,287,354 cohort participants, 51% lived within the modeled area. For the cancer cases, this figure was 52%. 1,095,234 of all children were exposed to a RF-EMF exposure below 0.05 V/m, 142,770 to a RF-EMF exposure between 0.05 and 0.2 V/m and 49,350 children to a RF-EMF exposure above 0.2 V/m. **Figure 2** shows the total field levels by distance to the closest transmitter for all residencies in the modeled study area. Spearman correlation between total field levels and distance to the closest transmitter was -0.462 (95%-CI: -0.464, -0.460). Arithmetic mean exposure in the whole study sample within the modeled area was 0.14 V/m with a median value of 0.02 V/m, a $90^{th}$ percentile of 0.16 V/m and a maximum of 9.77 V/m. Mean exposure was higher in urban areas (0.17 V/m) than in suburban areas (0.14 V/m) and in rural areas (0.08 V/m).

Results from the time to event analysis are shown in **Table 1** and **Figure 3.** Compared to the group of children exposed to a RF-EMF below 0.05 V/m, hazard ratios (HR) for the highest exposure category (≥ 0.2 V/m) were 1.03 (95% CI 0.74, 1.43) for all cancers, 0.55 (95%-CI: 0.26, 1.19) for leukemia, 0.61 (95%-CI: 0.27, 1.41) for ALL and 1.71 (95% CI 0.99, 2.94) for CNS tumors when considering all transmitters. These results were similar when restricting the

analyses to VHF- and UHF-transmitters (**Table 1).** Somewhat higher hazard ratios were found for all types of cancer for short and medium wave transmitters. However, this result was based on 13 exposed cases only. Within the 95% confidence bands results were similar for both age groups (**Figure 3**). The linear exposure response analyses provided a similar result pattern as the categorical analyses although the positive correlation with CNS tumours and the negative correlation with leukemia reached statistical significance for all types of transmitters (**Table 2**). The linear analyses also indicated that none of the additional potential confounding factors materially altered the HRs (**Figure 4**). However, the factors for which we decided *a priori* to adjust for (benzene exposure, exposure to background gamma radiation, distance to high voltage power lines) showed a larger change in the hazard ratios in the analyses with categorical exposure classification. Restricting the analysis to children, who were living within the modeled exposure area of the radio and TV transmitters (**Web Table 1**) or additionally considering 51 cancer cases with known place of residence but not linkable to the SNC data (**Web Table 2**) had virtually no impact on the results.

For the aggregated resident cohort analysis we identified 4,486 eligible cancer cases in the SCCR. Of these, 244 cases were excluded due to missing geo-coded address at diagnosis. Of the 4,246 included cases, considered for the resident cohort, 1,326 were diagnosed with leukemia (1,062 ALL) and 859 cases with a CNS tumor. Results for the age-stratified analyses are shown in **Table 3** and **Figure 5.** Again leukemia tended to be negatively correlated with RF-EMF reaching statistical significance in the highest exposure category for the older age groups with respect to exposure from all transmitters (IRR=0.44, 95%-CI: 0.24, 0.8). CNS tumor risk was not related to RF-EMF from all transmitters in any of the age groups. Analyses of the resident cohort restricted for the period before 1995 yielded, however, increased incident rate ratios in the high exposure category for the younger age group for all cancer (IRR=1.61; 95%: 1.19, 2.16), ii), leukemia (IRR =1.57, 95%-CI: 0.96, 2.57), ALL

(IRR =1.79; 95%: 1.07, 2.97) and CNS tumors (IRR=2.42; 95%-CI: 1.22-4.81) (**Table 4**). After 1995 all IRR in this age group were below unity.

## DISCUSSION

This large census based cohort study does not indicate increased childhood leukemia risk from RF-EMF exposure of broadcasting. We observed, however, elevated risks for CNS tumors in some of the analyses.

The main strength of this study was that it was based on census data and cancer cases from registries, without the requirement to contact study participants. As a consequence a high proportion of all eligible study participants could be included which prevents from participation bias. In addition, we were able to individually assess RF-EMF exposure based on established models and did not have to rely on rough exposure proxies such as distance, which have been used in many previous studies (6-8, 10-13, 15). Exposure distribution of radio and TV transmitters is far more complex and our analyses indicated only a moderate correlation between the modeled field strengths and the distance to the nearest broadcast transmitters. A recent letter criticized distance-based approaches, indicating that such approaches would be a good proxy for each single transmitter but not for all transmitters combined (38). This is especially the case for overlapping calculated areas where only modeled field strengths allow the consideration of the cumulative exposure to different broadcast transmitters. We applied two cohort analysis approaches, both with advantages and disadvantages. The time-to-event analysis allowed the consideration of numerous potential confounding factors, which has not been done in the two previous case-control studies (12-14). With this approach we could demonstrate that the evaluated confounding factors are not crucial for this type of exposure-response analysis. Thus, our second approach with basic

confounding adjustment in the resident cohort is considered reliable. The resident cohort covered a longer follow-up period and included more cancer cases, making this study the largest conducted so far on this topic with more than 4,000 childhood cancer cases. A further strength of the aggregated analysis was to consider separately data before 1995, when use of cordless and mobile phones was less prevalent and broadcast transmitter emission contributed to a larger proportion to the overall RF-EMF exposure of the population reducing the potential for exposure misclassification. Ideally, for the period after 1995 exposure contribution from wireless phone use and mobile phone base station would be considered in the analyses. However, this is very complex and data on cordless phone and mobile phone use are not available in this nation-wide cohort. Assessing long term exposure from mobile phone base station is almost impossible because of the high spatial variability and the rapid changes in the network during the last two decades. However, unless these new exposure sources are correlated with RF-EMF from broadcast transmitters, results are not biased but only reduced in statistical power.

Another limitation in the resident cohort analysis is the estimation of aggregated person-years by linearly intra- and extrapolating census data from 1990 and 2000. This introduces some uncertainty in the denominator of the incidence rate ratio calculations. Nevertheless, even an error of 10% in the denominator would not markedly change the calculated incidence rate ratios. Thus, this estimation process cannot have heavily affected the risk estimates.

Modeling of the field strengths is complex, especially for short and medium-wave transmitters, due to imprecise available information on input data, mainly the emission pattern of the transmitters over time. We had only data available from two years during the study period. In principle, one also needs to take into account local meteorology, morphology and soil conductivity for accurate modeling, which was not possible for the whole study period. These uncertainties concern particularly high exposure values. It was further not accounted

for vegetation or buildings when modeling field strength that are probably also important factors in terms of shielding, diffraction or the reflection of RF-EMF (4). For this reason we decided to conduct the primary analysis based on categorized exposure data, which is a more robust approach when there are outliers. As cases and healthy children are likewise affected, non-differential exposure misclassification would be expected to attenuate exposure-response associations.

In general exposure levels were relatively low and the number of study participants exposed above 0.2 V/m was small (4% of the study participants) especially for the time-to-event analysis. The aggregated analysis had a higher statistical power, but the number of cases in the highest exposure group still remained small when conducting separate analyses for pre-school children and school children, or for specific time periods.

Our study showed no indications for an increased leukemia risk with respect to RF-EMF exposure from broadcast transmitters. The only positive association was seen in a subgroup of 0-4 year old children when restricting the analyses to the period before 1995. A lack of associations is in line with two previous case-control studies (12-14) with similar methodological features. Second, animal, in-vitro and laboratory studies did not find a biological mechanism for long-term exposure to low levels of RF-EMF (1, 39, 40).

With respect to CNS tumor our results are less clear. Indications of an association with RF-EMF were found both in the time-to-event analysis and in the aggregated cohort analyses restricted to the younger age group and the time period prior to 1995. However, incidence rate ratios were not increased for the entire aggregate cohort analysis comprising the whole study period from 1985 to 2008. This aggregate cohort analysis is based on the highest number of exposed cases and thus may be considered most reliable, whereas chance might be an explanation for the observed associations in the smaller datasets. It may also be speculated

that before 1995 diagnosis of cancer occurred in urban areas in an earlier disease status compared to rural areas. This would shift in urban areas, where RF-EMF exposure is higher on average, cases from the older age group to the younger group. Such a mechanism could explain the observed pattern in the aggregate cohort analysis. On the other hand a causal interpretation may be supported if one gives more weight to the data before 1995 where exposure misclassification is reduced. An alternative explanation for the differences between the time-to-event and the aggregated cohort analysis may be the biologically relevant exposure time window. The time-to-event analysis considered exposure at baseline at the time of census 2000 whereas the aggregated analyses considered exposure at time of diagnosis. A potentially relevant latency time between exposure and disease is more likely to be captured with the first approach estimating exposure at baseline.

In depth analyses of the statistically significant linear exposure-response in the time-to-event analysis revealed that the result was strongly affected by two highly exposed (> 1 V/m) cases (0.8% of all cases), compared to only 0.1% of the study participants exposed above this level. Because no highly exposed leukemia case was observed, confidence intervals of the CNS analyses were considerable narrower than for the leukemia analyses despite similar number of cases.

Our CNS results contradict the result from a Korean case-control study on broadcast transmitters (12, 13) and a British case-control study on mobile phone base station exposure (41). If low RF-EMF levels as observed in our study would cause CNS tumors in children, one would also expect increased risks from use of wireless phones, which lead to substantially higher exposure to the head. However, such an association was not observed in a previous case-control study (42). CNS tumor incidence rates have not been found to increase in 7-19 year old children in Northern European countries between 1990 and 2009 (43). Finally,

neither animal nor in-vivo or in-vitro studies have identified a mechanism which would support an association at these low RF-EMF levels (1, 44).

In summary, this study provides evidence that childhood leukemia is not related to RF-EMF exposure from broadcast transmitters. Results for CNS tumors were less consistent and need further clarification.

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## FIGURE CAPTIONS

**FIGURE 1. Linkage of the database of the Swiss Childhood Cancer registry to the Swiss National Cohort. ALL= acute lymphoblastic leukemia, CNS = central nervous system**

**FIGURE 2. Scatter plot of modeled field strengths versus distance of children's households to the nearest broadcast transmitter within the modeled areas**

**FIGURE 3: Hazard ratios (HR) from the time-to-event analyses for RF-EMF from all transmitters adjusted for age, gender, environmental gamma radiation and benzene exposure and period effects**

**FIGURE 4: Effect of confounding adjustment on the linear regression coefficient (HR per 0.1 V/m exposure increase) in the time-to-event analysis. Potential confounding factors were included in the full model one at a time.**

**FIGURE 5: IRRs from the aggregated cohort analysis for RF-EMF exposure from all transmitters adjusted for age, calendar year and gender**

# TABLES

**Table 1: Time-to-Event Analysis: Hazard Ratios(HR) by Exposure Categories from Cox Regression, Switzerland, 2000-2008**

| | Age 0-16 years | | | | | Age 0-4 years | | | Age 5-15 years | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cases | baseline HR[a] | 95% CI | HR[b] | 95% CI | Cases | HR[b] | 95% CI | Cases | HR[b] | 95% CI |
| **All transmitters** | | | | | | | | | | | |
| *All cancers* | | | | | | | | | | | |
| <0.05 V/m | 830 | 1 | Referent | | | 140 | 1 | Referent | 690 | 1 | Referent |
| 0.05-0.2 V/m | 127 | 1.17 | 0.97, 1.40 | 1.15 | 0.95, 1.39 | 24 | 1.22 | 0.78, 1.90 | 103 | 1.13 | 0.92, 1.40 |
| >0.2 V/m | 40 | 1.06 | 0.77, 1.45 | 1.03 | 0.74, 1.43 | 6 | 0.82 | 0.36, 1.91 | 34 | 1.08 | 0.76, 1.54 |
| *All Leukemias* | | | | | | | | | | | |
| <0.05 V/m | 251 | 1 | Referent | 1 | Referent | 64 | 1 | Referent | 187 | 1 | Referent |
| 0.05-0.2 V/m | 25 | 0.75 | 0.50, 1.13 | 0.71 | 0.46, 1.08 | 7 | 0.72 | 0.32, 1.61 | 18 | 0.70 | 0.43, 1.15 |
| >0.2 V/m | 7 | 0.60 | 0.28, 1.28 | 0.55 | 0.26, 1.19 | 1 | 0.26 | 0.04, 1.95 | 6 | 0.67 | 0.29, 1.54 |
| *ALL* | | | | | | | | | | | |
| <0.05 V/m | 199 | 1 | Referent | 1 | Referent | 56 | 1 | Referent | 143 | 1 | Referent |
| 0.05-0.2 V/m | 20 | 0.76 | 0.48, 1.20 | 0.73 | 0.45, 1.16 | 5 | 0.60 | 0.24, 1.53 | 15 | 0.78 | 0.45, 1.34 |
| >0.2 V/m | 6 | 0.65 | 0.29, 1.46 | 0.61 | 0.27, 1.41 | 1 | 0.32 | 0.04, 2.36 | 5 | 0.75 | 0.30, 1.87 |
| *CNS-tumors* | | | | | | | | | | | |
| <0.05 V/m | 207 | 1 | Referent | 1 | Referent | 33 | 1 | Referent | 174 | 1 | Referent |
| 0.05-0.2 V/m | 36 | 1.32 | 0.93, 1.89 | 1.38 | 0.96, 1.99 | 7 | 1.80 | 0.77, 4.16 | 29 | 1.31 | 0.87, 1.96 |
| >0.2 V/m | 15 | 1.59 | 0.94, 2.68 | 1.71 | 0.99, 2.94 | 2 | 1.68 | 0.39, 7.36 | 13 | 1.70 | 0.95, 3.06 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **VHF- and UHF-transmitters** | | | | | | | | | | | |
| *All cancers* | | | | | | | | | | | |
| <0.05 V/m | 841 | 1 | Referent | 1 | Referent | 143 | 1 | Referent | 698 | 1 | Referent |
| 0.05-0.2 V/m | 117 | 1.15 | 0.95, 1.40 | 1.13 | 0.93, 1.38 | 22 | 1.17 | 0.73, 1.86 | 95 | 1.12 | 0.90, 1.40 |
| >0.2 V/m | 39 | 1.04 | 0.75, 1.43 | 1.01 | 0.73, 1.41 | 5 | 0.68 | 0.27, 1.69 | 34 | 1.09 | 0.76, 1.55 |
| *All Leukemias* | | | | | | | | | | | |
| <0.05 V/m | 255 | 1 | Referent | 1 | Referent | 65 | 1 | Referent | 190 | 1 | Referent |
| 0.05-0.2 V/m | 21 | 0.67 | 0.43, 1.05 | 0.63 | 0.40, 0.99 | 6 | 0.65 | 0.27, 1.53 | 15 | 0.62 | 0.36, 1.06 |
| >0.2 V/m | 7 | 0.61 | 0.29, 1.28 | 0.55 | 0.25, 1.18 | 1 | 0.26 | 0.04, 1.93 | 6 | 0.67 | 0.29, 1.53 |
| *ALL* | | | | | | | | | | | |
| <0.05 V/m | 201 | 1 | Referent | 1 | Referent | 56 | 1 | Referent | 145 | 1 | Referent |
| 0.05-0.2 V/m | 18 | 0.73 | 0.45, 1.18 | 0.70 | 0.43, 1.14 | 5 | 0.65 | 0.25, 1.65 | 13 | 0.72 | 0.40, 1.29 |
| >0.2 V/m | 6 | 0.66 | 0.29, 1.48 | 0.62 | 0.27, 1.42 | 1 | 0.32 | 0.04, 2.42 | 5 | 0.75 | 0.30, 1.87 |
| *CNS-tumors* | | | | | | | | | | | |
| <0.05 V/m | 210 | 1 | Referent | 1 | Referent | 34 | 1 | Referent | 176 | 1 | Referent |
| 0.05-0.2 V/m | 34 | 1.34 | 0.93, 1.92 | 1.40 | 0.96, 2.04 | 7 | 1.89 | 0.81, 4.42 | 27 | 1.31 | 0.86, 2.00 |
| >0.2 V/m | 14 | 1.49 | 0.87, 2.56 | 1.60 | 0.91, 2.81 | 1 | 0.82 | 0.11, 6.21 | 13 | 1.72 | 0.96, 3.10 |
| **Short and medium wave transmitters** | | | | | | | | | | | |
| *All cancers* | | | | | | | | | | | |
| <0.05 V/m | 984 | 1 | Referent | 1 | Referent | 166 | 1 | Referent | 818 | 1 | Referent |
| >0.05 V/m | 13 | 1.49 | 0.86, 2.58 | 1.48 | 0.86, 2.56 | 4 | 2.74 | 1.01, 7.41 | 9 | 1.23 | 0.64, 2.38 |
| *All Leukemias* | | | | | | | | | | | |
| <0.05 V/m | 278 | 1 | Referent | 1 | Referent | 70 | 1 | Referent | 208 | 1 | Referent |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| >0.05 V/m | 5 | 2.03 | 0.84, 4.92 | 2.00 | 0.82, 4.84 | 2 | 3.30 | 0.80, 13.54 | 3 | 1.59 | 0.51, 4.98 |
| *ALL* | | | | | | | | | | | |
| <0.05 V/m | 222 | 1 | Referent | 1 | Referent | 61 | 1 | Referent | 161 | 1 | Referent |
| >0.05 V/m | 3 | 1.53 | 0.49, 4.77 | 1.48 | 0.47, 4.63 | 1 | 1.81 | 0.25, 13.15 | 2 | 1.36 | 0.34, 5.48 |
| *CNS-tumors* | | | | | | | | | | | |
| <0.05 V/m | 255 | 1 | Referent | 1 | Referent | 41 | 1 | Referent | 214 | 1 | Referent |
| >0.05 V/m | 3 | 1.33 | 0.43, 4.15 | 1.30 | 0.42, 4.07 | 1 | 2.70 | 0.37, 19.74 | 2 | 1.04 | 0.26, 4.18 |

Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval; CNS tumors, central nervous system tumors; HR, hazard ratio

[a] adjusted for gender and period effects while using age as the underlying time scale

[b] additionally adjusted for the environmental gamma radiation, benzene exposure and distance to the next high voltage power line

**Table 2: Time-to-Event Analysis: Hazard Ratios(HR) from Cox regression: Linear Dose-Response Analysis, Switzerland, 2000-2008**

| | Age 0-16 years | | | | | Age 0-4 years | | | Age 5-15 years | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Cases** | **baseline HR[a]** | **95% CI** | **HR[b]** | **95% CI** | **Cases** | **HR[a]** | **95% CI** | **Cases** | **HR[a]** | **95% CI** |
| **All transmitters** | | | | | | | | | | | |
| *All cancers* | | | | | | | | | | | |
| per 0.1 V/m | 997 | 1.02 | 0.97, 1.08 | 1.02 | 0.96, 1.08 | 170 | 0.97 | 0.82, 1.16 | 827 | 1.03 | 0.97, 1.09 |
| *All Leukemias* | | | | | | | | | | | |
| per 0.1 V/m | 283 | 0.85 | 0.70, 1.03 | 0.82 | 0.67, 1.01 | 72 | 0.70 | 0.43, 1.15 | 211 | 0.86 | 0.69, 1.08 |
| ALL | | | | | | | | | | | |
| per 0.1 V/m | 225 | 0.89 | 0.73, 1.08 | 0.88 | 0.71, 1.08 | 62 | 0.70 | 0.41, 1.20 | 163 | 0.93 | 0.75, 1.16 |
| *CNS-tumors* | | | | | | | | | | | |
| per 0.1 V/m | 258 | 1.05 | 1.00, 1.10 | 1.05 | 1.00, 1.10 | 42 | 1.04 | 0.92, 1.18 | 216 | 1.06 | 1.00, 1.11 |
| **VHF- and UHF-transmitters** | | | | | | | | | | | |
| *All cancers* | | | | | | | | | | | |
| per 0.1 V/m | 997 | 1.02 | 0.97, 1.08 | 1.02 | 0.96, 1.08 | 170 | 0.96 | 0.79, 1.15 | 827 | 1.03 | 0.97, 1.09 |
| All Leukemias | | | | | | | | | | | |
| per 0.1 V/m | 283 | 0.85 | 0.70, 1.03 | 0.82 | 0.67, 1.01 | 72 | 0.72 | 0.44, 1.16 | 211 | 0.86 | 0.68, 1.08 |
| *ALL* | | | | | | | | | | | |
| per 0.1 V/m | 225 | 0.90 | 0.74, 1.09 | 0.89 | 0.72, 1.09 | 62 | 0.73 | 0.43, 1.22 | 163 | 0.93 | 0.75, 1.16 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *CNS-tumors* | | | | | | | | | | | |
| per 0.1 V/m | 258 | 1.05 | 1.00, 1.10 | 1.05 | 1.00, 1.10 | 42 | 1.02 | 0.83, 1.27 | 216 | 1.06 | 1.01, 1.11 |
| **Short and medium wave transmitters** | | | | | | | | | | | |
| *All cancers* | | | | | | | | | | | |
| per 0.1 V/m | 997 | 1.05 | 0.86, 1.27 | 1.05 | 0.86, 1.27 | 170 | 1.62 | 0.92, 2.85 | 827 | 0.98 | 0.59, 1.64 |
| *All Leukemias* | | | | | | | | | | | |
| per 0.1 V/m | 283 | 0.89 | 0.29, 2.73 | 0.89 | 0.28, 2.76 | 72 | 0.99 | 0.12, 7.92 | 211 | 0.85 | 0.22, 3.31 |
| *ALL* | | | | | | | | | | | |
| per 0.1 V/m | 225 | 0.65 | 0.14, 3.05 | 0.63 | 0.13, 3.00 | 62 | 0.63 | 0.03, 12.40 | 163 | 0.63 | 0.10, 3.94 |
| *CNS-tumors* | | | | | | | | | | | |
| per 0.1 V/m | 258 | 1.07 | 0.82, 1.38 | 1.06 | 0.81, 1.39 | 42 | 2.05 | 1.20, 3.51 | 216 | 0.56 | 0.11, 2.99 |

Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval; CNS tumors, central nervous system tumors; HR, hazard ratio

[a] adjusted for gender and period effects while using age as the underlying time scale

[b] additionally adjusted for the environmental gamma radiation, benzene exposure and distance to the next high voltage power line

**Table 3: Poisson Resident Cohort Analysis: Incidence Rate Ratios (IRR) by Exposure Categories from 1985-2008.**

| | Age 0-16 years | | | Age 0-4 years | | | Age 5-15 years | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Cases** | **IRR[a]** | **95% CI** | **Cases** | **IRR[a]** | **95% CI** | **Cases** | **IRR[a]** | **95% CI** |
| **All transmitters** | | | | | | | | | |
| *All cancers* | | | | | | | | | |
| <0.05 V/m | 3,591 | 1 | Referent | 1,569 | 1 | Referent | 2,022 | 1 | Referent |
| 0.05-0.2 V/m | 511 | 1.09 | 1.00, 1.20 | 225 | 1.08 | 0.94, 1.24 | 286 | 1.11 | 0.98, 1.25 |
| >0.2 V/m | 144 | 0.90 | 0.76, 1.06 | 80 | 1.11 | 0.89, 1.39 | 64 | 0.72 | 0.56, 0.93 |
| *All Leukemias* | | | | | | | | | |
| <0.05 V/m | 1,149 | 1 | Referent | 583 | 1 | Referent | 566 | 1 | Referent |
| 0.05-0.2 V/m | 138 | 0.92 | 0.77, 1.10 | 71 | 0.92 | 0.72,1.18 | 67 | 0.93 | 0.72, 1.19 |
| >0.2 V/m | 39 | 0.76 | 0.55, 1.05 | 28 | 1.06 | 0.72,1.55 | 11 | 0.44 | 0.24, 0.80 |
| *ALL* | | | | | | | | | |
| <0.05 V/m | 917 | 1 | Referent | 485 | 1 | Referent | 432 | 1 | Referent |
| 0.05-0.2 V/m | 112 | 0.94 | 0.77, 1.14 | 63 | 0.99 | 0.76,1.28 | 49 | 0.89 | 0.66, 1.19 |
| >0.2 V/m | 33 | 0.81 | 0.57, 1.14 | 24 | 1.09 | 0.73,1.65 | 9 | 0.47 | 0.25, 0.92 |
| *CNS tumors* | | | | | | | | | |
| <0.05 V/m | 718 | 1 | Referent | 235 | 1 | Referent | 483 | 1 | Referent |
| 0.05-0.2 V/m | 108 | 1.16 | 0.95, 1.42 | 37 | 1.18 | 0.83,1.67 | 71 | 1.15 | 0.90, 1.48 |
| >0.2 V/m | 33 | 1.03 | 0.73, 1.46 | 14 | 1.29 | 0.75,2.21 | 19 | 0.90 | 0.57, 1.42 |
| **VHF- and UHF-transmitters** | | | | | | | | | |
| *All cancers* | | | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| <0.05 V/m | 3,625 | 1 | Referent | 1,584 | 1 | Referent | 2,041 | 1 | Referent |
| 0.05-0.2 V/m | 479 | 1.11 | 1.01, 1.22 | 212 | 1.10 | 0.95, 1.27 | 267 | 1.12 | 0.99, 1.27 |
| >0.2 V/m | 142 | 0.89 | 0.75, 1.06 | 78 | 1.09 | 0.87, 1.37 | 64 | 0.73 | 0.57, 0.94 |
| *All Leukemias* | | | | | | | | | |
| <0.05 V/m | 1,159 | 1 | Referent | 587 | 1 | Referent | 572 | 1 | Referent |
| 0.05-0.2 V/m | 128 | 0.93 | 0.77, 1.11 | 67 | 0.94 | 0.73, 1.21 | 61 | 0.91 | 0.70, 1.19 |
| >0.2 V/m | 39 | 0.77 | 0.56, 1.06 | 28 | 1.07 | 0.73, 1.57 | 11 | 0.45 | 0.25, 0.81 |
| *ALL* | | | | | | | | | |
| <0.05 V/m | 922 | 1 | Referent | 487 | 1 | Referent | 435 | 1 | Referent |
| 0.05-0.2 V/m | 107 | 0.97 | 0.80, 1.19 | 61 | 1.04 | 0.79, 1.35 | 46 | 0.90 | 0.67, 1.22 |
| >0.2 V/m | 33 | 0.82 | 0.58, 1.16 | 24 | 1.11 | 0.74, 1.67 | 9 | 0.48 | 0.25, 0.93 |
| *CNS tumors* | | | | | | | | | |
| <0.05 V/m | 724 | 1 | Referent | 237 | 1 | Referent | 487 | 1 | Referent |
| 0.05-0.2 V/m | 102 | 1.18 | 0.96, 1.46 | 35 | 1.20 | 0.84, 1.72 | 67 | 1.18 | 0.91, 1.52 |
| >0.2 V/m | 33 | 1.04 | 0.73, 1.48 | 14 | 1.30 | 0.76, 2.23 | 19 | 0.91 | 0.57, 1.44 |
| Short and medium wave transmitters | | | | | | | | | |
| **All cancers** | | | | | | | | | |
| <0.05 V/m | 4,205 | 1 | Referent | 1,854 | 1 | Referent | 2,351 | 1 | Referent |
| >0.05 V/m | 41 | 1.07 | 0.78, 1.45 | 20 | 1.18 | 0.76, 1.84 | 21 | 0.97 | 0.63, 1.50 |
| *All Leukemias* | | | | | | | | | |
| <0.05 V/m | 1,312 | 1 | Referent | 675 | 1 | Referent | 637 | 1 | Referent |
| >0.05 V/m | 14 | 1.16 | 0.69, 1.97 | 7 | 1.14 | 0.54, 2.39 | 7 | 1.19 | 0.57, 2.51 |
| *ALL* | | | | | | | | | |
| <0.05 V/m | 1,053 | 1 | Referent | 567 | 1 | Referent | 486 | 1 | Referent |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| >0.05 V/m | 9 | 0.93 | 0.48, 1.80 | 5 | 0.97 | 0.40, 2.33 | 4 | 0.89 | 0.33, 2.39 |
| *CNS tumors* | | | | | | | | | |
| <0.05 V/m | 852 | 1 | Referent | 283 | 1 | Referent | 569 | 1 | Referent |
| >0.05 V/m | 7 | 0.91 | 0.43, 1.91 | 3 | 1.18 | 0.38, 3.67 | 4 | 0.77 | 0.29, 2.07 |

Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval; CNS tumors, central nervous system tumors; IRR, incidence rate ratio

[a] adjusted for age, calendar year and gender

**Table 4: Incidence Rate Ratios (IRR) by Exposure Categories from the Resident Cohort, stratified for the period before and after 1995.**

| | Age 0-16 years | | | Age 0-4 years | | | Age 5-15 years | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Cases** | **IRR[a]** | **95% CI** | **Cases** | **IRR[a]** | **95% CI** | **Cases** | **IRR[a]** | **95% CI** |
| **1985-1995** | | | | | | | | | |
| **All transmitters** | | | | | | | | | |
| *All cancers* | | | | | | | | | |
| <0.05 V/m | 1,433 | 1 | Referent | 673 | 1 | Referent | 760 | 1 | Referent |
| 0.05-0.2 V/m | 202 | 1.11 | 0.96, 1.28 | 90 | 1.05 | 0.84, 1.31 | 112 | 1.16 | 0.95, 1.42 |
| >0.2 V/m | 76 | 1.23 | 0.98, 1.55 | 46 | 1.61 | 1.19, 2.16 | 30 | 0.91 | 0.63, 1.31 |
| *All Leukemias* | | | | | | | | | |
| <0.05 V/m | 478 | 1 | Referent | 255 | 1 | Referent | 223 | 1 | Referent |
| 0.05-0.2 V/m | 58 | 0.96 | 0.73, 1.26 | 28 | 0.87 | 0.59, 1.28 | 30 | 1.06 | 0.73, 1.55 |
| >0.2 V/m | 23 | 1.13 | 0.74, 1.71 | 17 | 1.57 | 0.96, 2.57 | 6 | 0.62 | 0.28, 1.40 |
| *ALL* | | | | | | | | | |
| <0.05 V/m | 378 | 1 | Referent | 212 | 1 | Referent | 166 | 1 | Referent |
| 0.05-0.2 V/m | 45 | 0.94 | 0.69, 1.28 | 25 | 0.93 | 0.62, 1.41 | 20 | 0.95 | 0.60, 1.52 |
| >0.2 V/m | 21 | 1.30 | 0.84, 2.02 | 16 | 1.79 | 1.07, 2.97 | 5 | 0.70 | 0.29, 1.70 |
| *CNS tumors* | | | | | | | | | |
| <0.05 V/m | 247 | 1 | Referent | 87 | 1 | Referent | 160 | 1 | Referent |
| 0.05-0.2 V/m | 35 | 1.12 | 0.78, 1.59 | 13 | 1.17 | 0.65, 2.10 | 22 | 1.08 | 0.69, 1.69 |
| >0.2 V/m | 17 | 1.60 | 0.98, 2.61 | 9 | 2.42 | 1.22, 4.81 | 8 | 1.15 | 0.57, 2.35 |
| **1996-2008** | | | | | | | | | |
| **All transmitters** | | | | | | | | | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| *All cancers* | | | | | | | | | |
| <0.05 V/m | 2,158 | 1 | Referent | 896 | 1 | Referent | 1,262 | 1 | Referent |
| 0.05-0.2 V/m | 309 | 1.09 | 0.96, 1.22 | 135 | 1.10 | 0.92, 1.31 | 174 | 1.08 | 0.92, 1.26 |
| >0.2 V/m | 68 | 0.69 | 0.57, 0.87 | 34 | 0.78 | 0.55, 1.10 | 34 | 0.61 | 0.44, 0.86 |
| *All Leukemias* | | | | | | | | | |
| <0.05 V/m | 671 | 1 | Referent | 328 | 1 | Referent | 343 | 1 | Referent |
| 0.05-0.2 V/m | 80 | 0.90 | 0.71, 1.14 | 43 | 0.96 | 0.70, 1.32 | 37 | 0.84 | 0.60, 1.18 |
| >0.2 V/m | 16 | 0.52 | 0.32, 0.85 | 11 | 0.70 | 0.38, 1.28 | 5 | 0.33 | 0.14, 0.80 |
| *ALL* | | | | | | | | | |
| <0.05 V/m | 539 | 1 | Referent | 273 | 1 | Referent | 266 | 1 | Referent |
| 0.05-0.2 V/m | 67 | 0.94 | 0.73, 1.21 | 38 | 1.02 | 0.73, 1.44 | 29 | 0.85 | 0.58, 1.24 |
| >0.2 V/m | 12 | 0.48 | 0.27, 0.86 | 8 | 0.61 | 0.30, 1.24 | 4 | 0.34 | 0.13, 0.91 |
| *CNS tumors* | | | | | | | | | |
| <0.05 V/m | 471 | 1 | Referent | 148 | 1 | Referent | 323 | 1 | Referent |
| 0.05-0.2 V/m | 73 | 1.18 | 0.92, 1.51 | 24 | 1.18 | 0.77, 1.82 | 49 | 1.18 | 0.87, 1.59 |
| >0.2 V/m | 16 | 0.75 | 0.45, 1.23 | 5 | 0.70 | 0.29, 1.70 | 11 | 0.77 | 0.42, 1.41 |

Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval; CNS tumors, central nervous system tumors; IRR, incidence rate ratio

[a] adjusted for age, calendar year and gender

## ONLINE SUPPLEMENTARY TABLES

**Web Table 1: Time-to-Event Analysis: Hazard Ratios(HR) by Exposure Categories from Cox regression: Children, Living Within the Modeled Exposure Area of Radio and TV Transmitters, Switzerland, 2000-2008**

| | Age 0-16 years | | | Age 0-4 years | | | Age 5-15 years | | |
|---|---|---|---|---|---|---|---|---|---|
| | Cases | HR[a] | 95% CI | Cases | HR[a] | 95% CI | Cases | HR[a] | 95% CI |
| **All transmitters** | | | | | | | | | |
| *All cancers* | | | | | | | | | |
| <0.05 V/m | 354 | 1 | Referent | 53 | 1 | Referent | 301 | 1 | Referent |
| 0.05-0.2 V/m | 127 | 1.16 | 0.94, 1.42 | 24 | 1.45 | 0.89, 2.36 | 103 | 1.11 | 0.88, 1.39 |
| >0.2 V/m | 40 | 1.06 | 0.76, 1.48 | 6 | 1.00 | 0.42, 2.36 | 34 | 1.07 | 0.75, 1.54 |
| *All Leukemias* | | | | | | | | | |
| <0.05 V/m | 92 | 1 | Referent | 26 | 1 | Referent | 66 | 1 | Referent |
| 0.05-0.2 V/m | 25 | 0.84 | 0.54, 1.31 | 7 | 0.82 | 0.35, 1.89 | 18 | 0.85 | 0.50, 1.44 |
| >0.2 V/m | 7 | 0.67 | 0.31, 1.47 | 1 | 0.30 | 0.04, 2.28 | 6 | 0.84 | 0.36, 1.98 |
| *ALL* | | | | | | | | | |
| <0.05 V/m | 70 | 1 | Referent | 25 | 1 | Referent | 45 | 1 | Referent |
| 0.05-0.2 V/m | 20 | 0.89 | 0.54, 1.47 | 5 | 0.62 | 0.24, 1.64 | 15 | 1.04 | 0.58, 1.87 |
| >0.2 V/m | 6 | 0.78 | 0.33, 1.82 | 1 | 0.35 | 0.05, 2.62 | 5 | 1.03 | 0.40, 2.66 |
| *CNS-tumors* | | | | | | | | | |
| <0.05 V/m | 89 | 1 | Referent | 13 | 1 | Referent | 76 | 1 | Referent |
| 0.05-0.2 V/m | 36 | 1.31 | 0.89, 1.94 | 7 | 1.91 | 0.74, 4.90 | 29 | 1.22 | 0.79, 1.88 |
| >0.2 V/m | 15 | 1.57 | 0.90, 2.76 | 2 | 1.76 | 0.38, 8.17 | 13 | 1.54 | 0.84, 2.83 |

Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval; CNS tumors, central nervous system tumors; HR, hazard ratio

[a] adjusted for the environmental gamma radiation, benzene exposure and distance to the next high voltage power line

**Web Table 2: Time-to-Event Analysis: Hazard Ratios(HR) by Exposure Categories from Cox regression: Consideration of an Additional 51 Cancer Cases Who Could not be Linked to the SNC but Whom Addresses Include the Date of Census 2000 /December 5th 2000), Switzerland, 2000-2008**

| | Age 0-16 years | | | Age 0-4 years | | | Age 5-15 years | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Cases** | **HR[a]** | **95% CI** | **Cases** | **HR[a]** | **95% CI** | **Cases** | **HR[a]** | **95% CI** |
| **All transmitters** | | | | | | | | | |
| *All cancers* | | | | | | | | | |
| <0.1 V/m | 874 | 1 | Referent | 146 | 1 | Referent | 728 | 1 | Referent |
| 0.1-0.3 V/m | 131 | 1.12 | 0.93, 1.36 | 25 | 1.22 | 0.79, 1.89 | 106 | 1.10 | 0.89, 1.36 |
| >0.3 V/m | 43 | 1.04 | 0.76, 1.43 | 7 | 0.92 | 0.42, 2.01 | 36 | 1.07 | 0.76, 1.51 |
| *All Leukemias* | | | | | | | | | |
| <0.05 V/m | 266 | 1 | Referent | 68 | 1 | Referent | 198 | 1 | Referent |
| 0.05-0.2 V/m | 25 | 0.66 | 0.43, 1.00 | 7 | 0.67 | 0.30, 1.49 | 18 | 0.66 | 0.40, 1.08 |
| >0.2 V/m | 7 | 0.50 | 0.23, 1.07 | 1 | 0.24 | 0.03, 1.80 | 6 | 0.60 | 0.26, 1.39 |
| *ALL* | | | | | | | | | |
| <0.05 V/m | 211 | 1 | Referent | 60 | 1 | Referent | 151 | 1 | Referent |
| 0.05-0.2 V/m | 20 | 0.67 | 0.42, 1.07 | 5 | 0.55 | 0.22, 1.40 | 15 | 0.72 | 0.42, 1.24 |
| >0.2 V/m | 6 | 0.54 | 0.24, 1.25 | 1 | 0.29 | 0.04, 2.13 | 5 | 0.66 | 0.27, 1.65 |
| *CNS-tumors* | | | | | | | | | |
| <0.05 V/m | 214 | 1 | Referent | 33 | 1 | Referent | 181 | 1 | Referent |
| 0.05-0.2 V/m | 38 | 1.41 | 0.99, 2.01 | 8 | 2.05 | 0.92, 4.56 | 30 | 1.30 | 0.87, 1.94 |
| >0.2 V/m | 15 | 1.64 | 0.95, 2.82 | 2 | 1.57 | 0.36, 6.84 | 13 | 1.65 | 0.92, 2.96 |

Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval; CNS tumors, central nervous system tumors; HR, hazard ratio

[a] adjusted for age, gender, period effects, the environmental gamma radiation and benzene exposure; no information on distance to next high voltage power line was available for the additional 51 cancer cases and thus, we did not adjust for this factor for these analyses

## FIGURES

### Figure 1

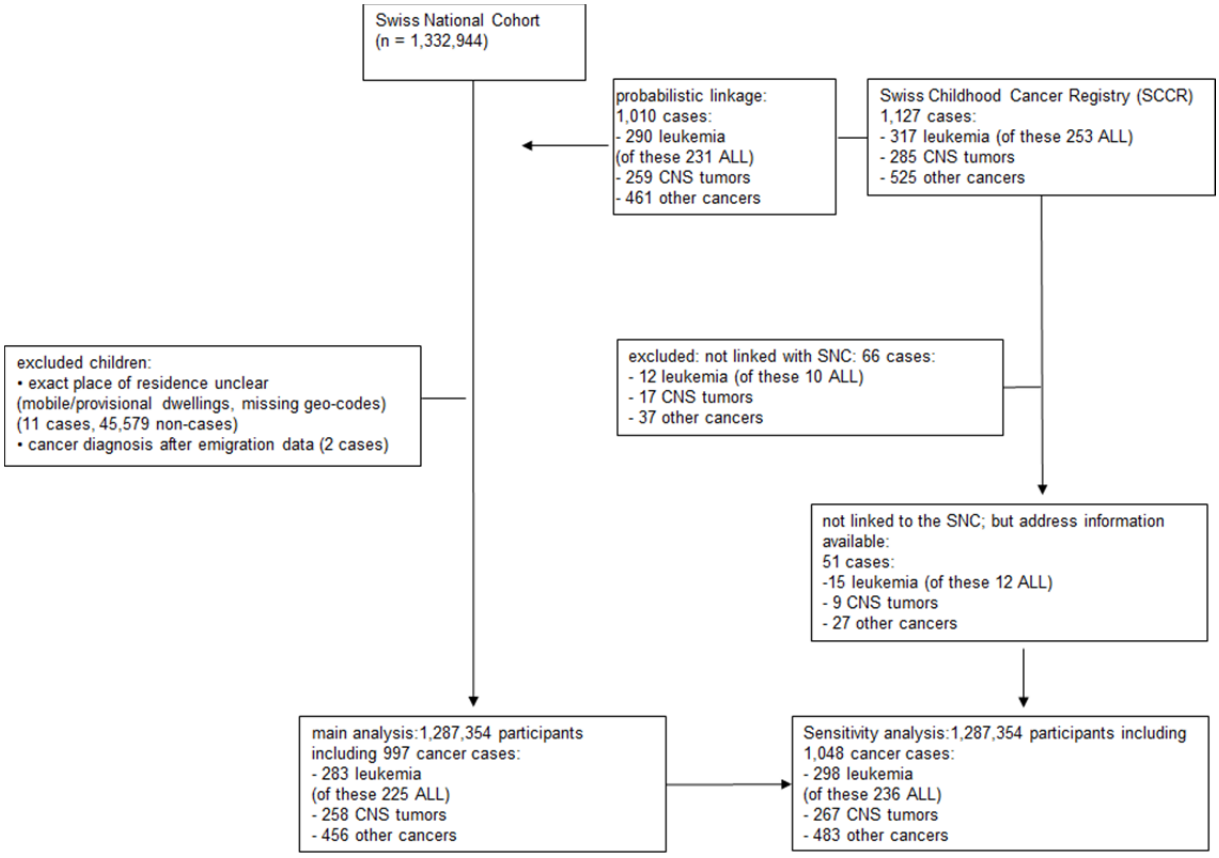
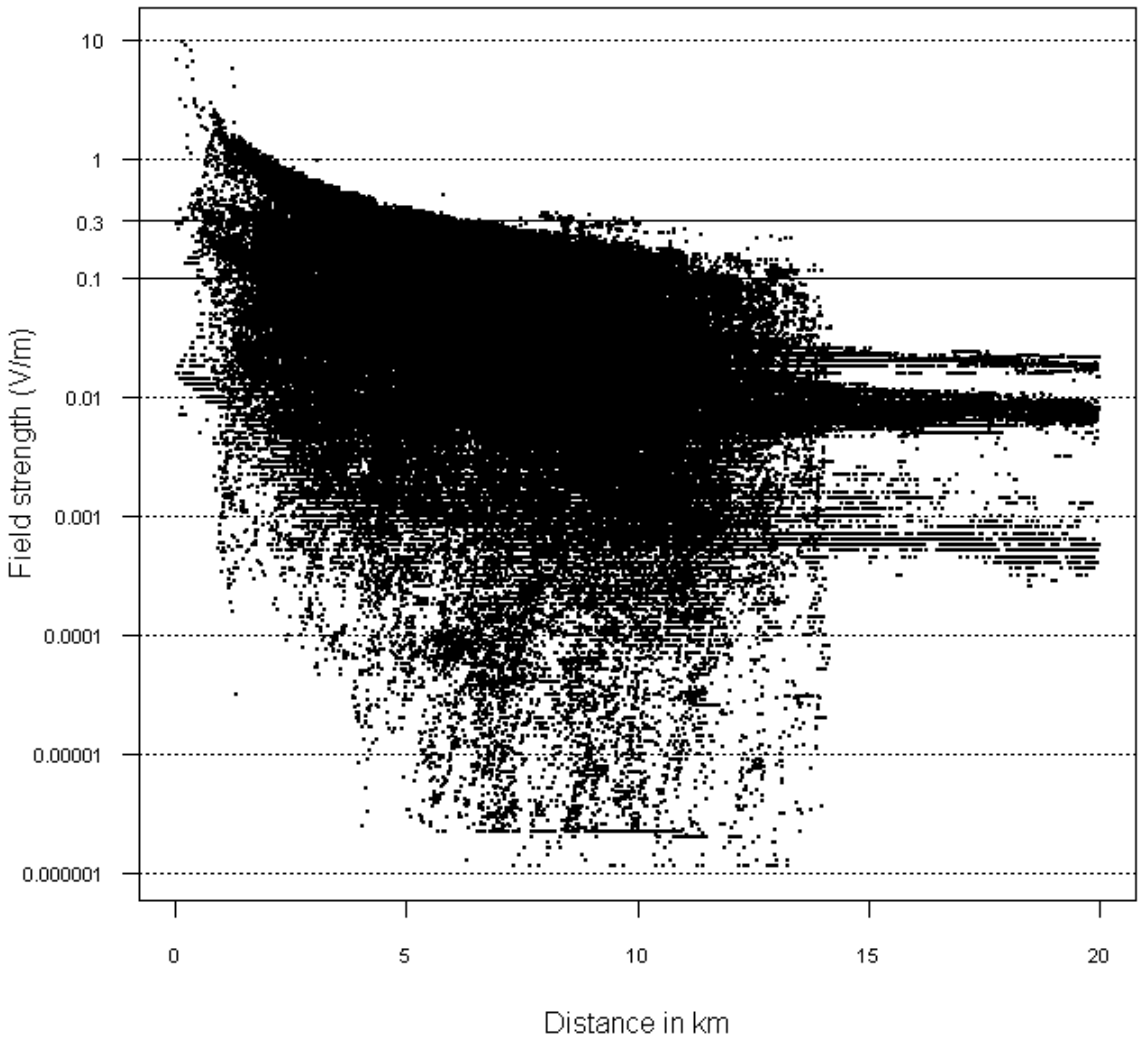
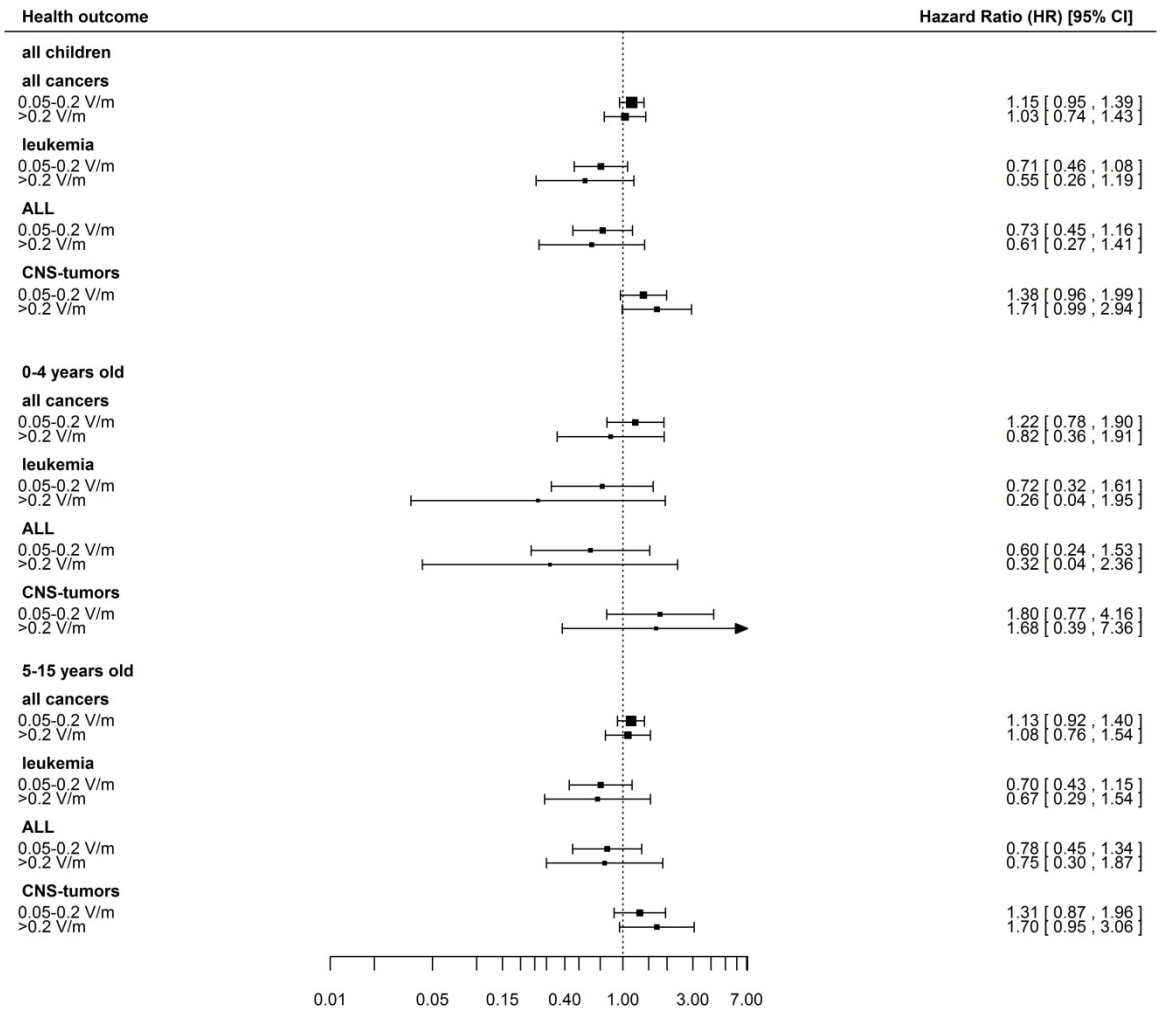


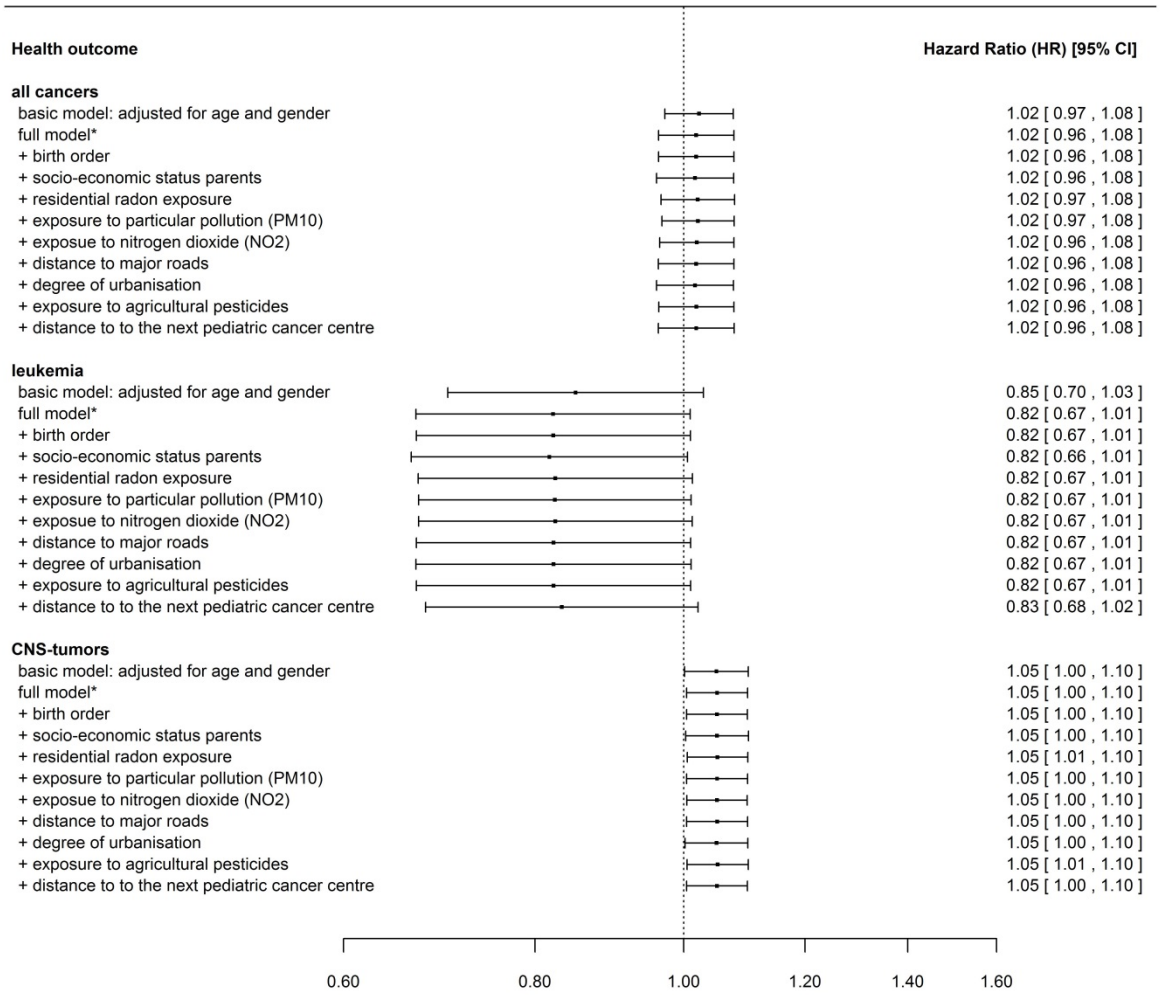
**Figure 2**


10
1
0.3
0.1
0.01
0.001
0.0001
0.00001
0.000001
Field strength (V/m)
0
5
10
15
20
Distance in km

## Figure 3


Health outcome
Hazard Ratio (HR) [95% CI]
all children
all cancers
0.05-0.2 V/m
1.15 [ 0.95 , 1.39 ]
>0.2 V/m
1.03 [ 0.74 , 1.43 ]
leukemia
0.05-0.2 V/m
0.71 [ 0.46 , 1.08 ]
>0.2 V/m
0.55 [ 0.26 , 1.19 ]
ALL
0.05-0.2 V/m
0.73 [ 0.45 , 1.16 ]
>0.2 V/m
0.61 [ 0.27 , 1.41 ]
CNS-tumors
0.05-0.2 V/m
1.38 [ 0.96 , 1.99 ]
>0.2 V/m
1.71 [ 0.99 , 2.94 ]
0-4 years old
all cancers
0.05-0.2 V/m
1.22 [ 0.78 , 1.90 ]
>0.2 V/m
0.82 [ 0.36 , 1.91 ]
leukemia
0.05-0.2 V/m
0.72 [ 0.32 , 1.61 ]
>0.2 V/m
0.26 [ 0.04 , 1.95 ]
ALL
0.05-0.2 V/m
0.60 [ 0.24 , 1.53 ]
>0.2 V/m
0.32 [ 0.04 , 2.36 ]
CNS-tumors
0.05-0.2 V/m
1.80 [ 0.77 , 4.16 ]
>0.2 V/m
1.68 [ 0.39 , 7.36 ]
5-15 years old
all cancers
0.05-0.2 V/m
1.13 [ 0.92 , 1.40 ]
>0.2 V/m
1.08 [ 0.76 , 1.54 ]
leukemia
0.05-0.2 V/m
0.70 [ 0.43 , 1.15 ]
>0.2 V/m
0.67 [ 0.29 , 1.54 ]
ALL
0.05-0.2 V/m
0.78 [ 0.45 , 1.34 ]
>0.2 V/m
0.75 [ 0.30 , 1.87 ]
CNS-tumors
0.05-0.2 V/m
1.31 [ 0.87 , 1.96 ]
>0.2 V/m
1.70 [ 0.95 , 3.06 ]
0.01
0.05
0.15
0.40
1.00
3.00
7.00

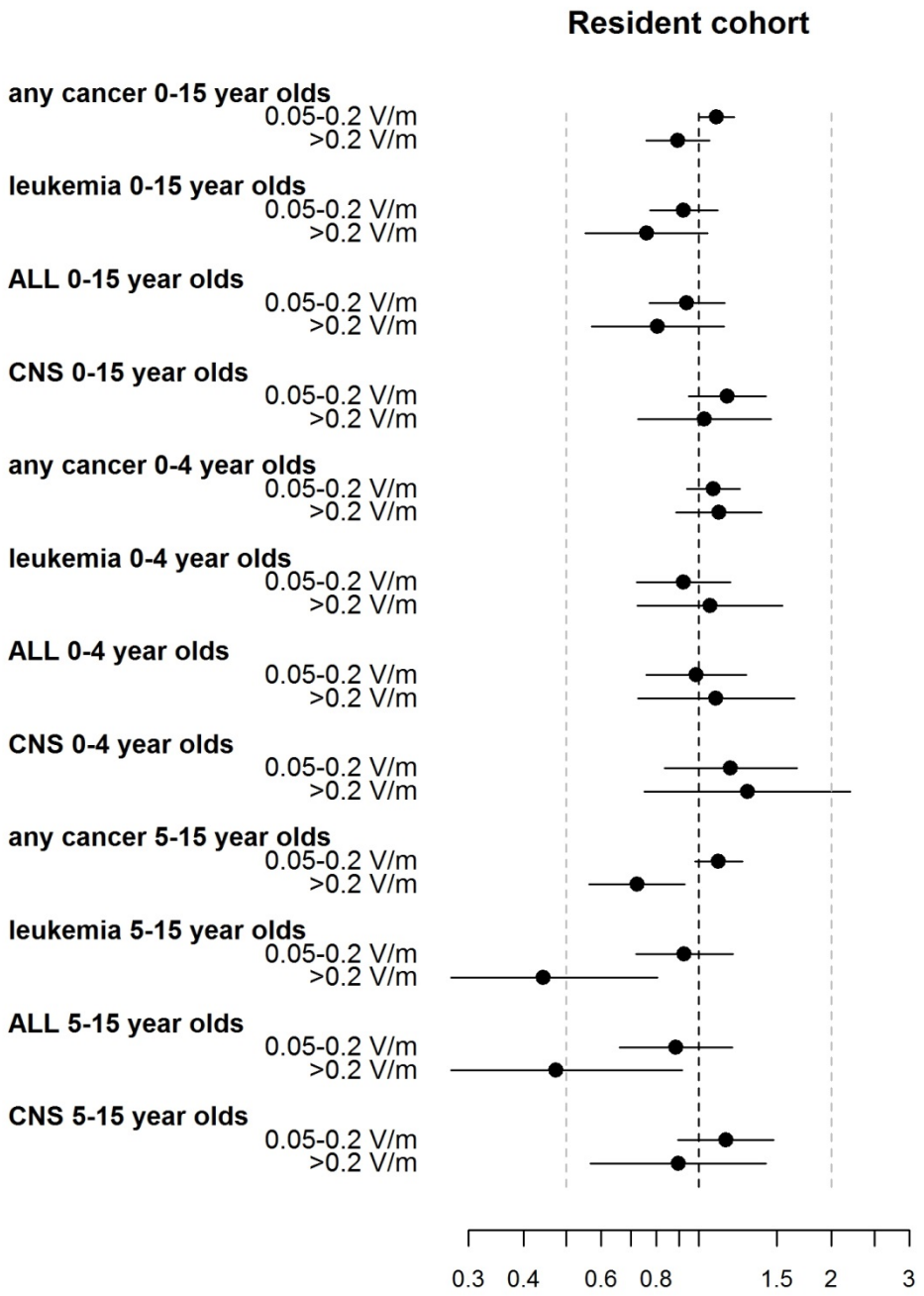
## Figure 4




* additionally adjusted for the environmental gamma radiation, benzene exposure and distance to the next high voltage power line

+ the relevance of additional potential confounding factors was tested by including one confounder at a time in the model, adjusted for age, gender, environmental gamma radiation, benzene exposure and distance to the next high voltage power line

**Figure 5**


Resident cohort
any cancer 0-15 year olds
0.05-0.2 V/m
>0.2 V/m
leukemia 0-15 year olds
0.05-0.2 V/m
>0.2 V/m
ALL 0-15 year olds
0.05-0.2 V/m
>0.2 V/m
CNS 0-15 year olds
0.05-0.2 V/m
>0.2 V/m
any cancer 0-4 year olds
0.05-0.2 V/m
>0.2 V/m
leukemia 0-4 year olds
0.05-0.2 V/m
>0.2 V/m
ALL 0-4 year olds
0.05-0.2 V/m
>0.2 V/m
CNS 0-4 year olds
0.05-0.2 V/m
>0.2 V/m
any cancer 5-15 year olds
0.05-0.2 V/m
>0.2 V/m
leukemia 5-15 year olds
0.05-0.2 V/m
>0.2 V/m
ALL 5-15 year olds
0.05-0.2 V/m
>0.2 V/m
CNS 5-15 year olds
0.05-0.2 V/m
>0.2 V/m
0.3
0.4
0.6
0.8
1.5
2
3

# 6 Summary of the main findings

This section summarises the results of each aim, formulated in chapter 2.2, and detailed in the corresponding articles.

**Aim 1: to assess whether domestic radon exposure is associated with childhood cancer**

***Objective 1:*** to develop a radon prediction model to estimate concentrations at households in Switzerland

In accordance with evidence from the literature, tectonic units and year of construction of the building were identified as the most important predictors in the final radon prediction model, followed by soil permeability, degree of urbanisation, floor of the building and housing type. These predictors were identified as important on the basis of the adjusted $R^2$, the AIC- and BIC-criteria and according to the evidence from the available literature. Our prediction model indicated that indoor radon concentrations are higher in regions with crystalline rocks (Alpine regions) and karst formations (Jurassic regions). Regions with karstified limestone and thus highly permeable rocks might be also characterised by high radon concentrations (62) provided that crystalline rocks are situated below the limestone in the regions. This is the case in the Jurassic regions in Switzerland. Radon levels are also increased in regions with a predominantly coarse soil texture compared to those with a fine soil texture. Lower radon concentrations were estimated in towns and cities compared to rural communities, and also for apartments compared to single family houses. Decreased radon levels were predicted for newer buildings and for upper floors.

The model was determined to be robust through validation with an independent dataset. Spearman rank correlation between measured and predicted values was 0.45 (95%-CI: 0.44, 0.46) for the model development set. Using a cut-off at the $90^{th}$ percentile, sensitivity was 31%, specificity 92%, Kappa coefficient 0.31 and the area under the ROC-curve was 0.73 (95%-CI: 0.72, 0.74). When validating the radon prediction model in the independent dataset, almost the same values for the Spearman rank correla-

tion, the sensitivity, the specificity, the Kappa coefficient and the area under the ROC-curve were received as for the development set. However, exposure misclassification is of concern for the highest exposure categories, expressed by the low sensitivity. The low $R^2$ is also of concern and was explained with inaccurate input data and the absence of data about relevant predictors, such as room ventilation or type of fundament.

Nevertheless, due to its robustness, the model was considered to be appropriate for predicting radon level exposure of the Swiss population in epidemiological research.

***Objective 2:*** to evaluate the model based exposure assessment: comparison with a measurement-based exposure assessment

The model-based approach and the measurement-based predictions provided similar results. The model-based approach yielded a mean radon exposure (arithmetic mean) of the Swiss population of 84.1 Bq/m³ (excluding inhabited basements) while an average exposure (arithmetic mean) of 78 Bq/m³ was derived from the measurement-based predictions. Both assessments found higher radon values for cantons in the Alpine and Jurassic region than in the Central Plateau. Spearman correlation between model-based and measurement-based predictions of arithmetic means at cantonal level was 0.70 (95%-CI: 0.41; 0.86). However, we found deviations between these two approaches attributed to the fact that in contrast to the measurement-based approach, the model-based predictions considered a broad spectrum of prediction factors. These are geologic and soil features but also different building characteristics. We estimated higher radon values for households in older buildings or detached houses but lower ones in apartments or in upper floors. Within municipality variability of these predictors was not accounted for in the measurement-based approach as it consisted only in averaging measurements within a municipality. Second, it became evident that the model-based approach does not depend on how measurement sites have been selected - the variance of the ratio between measured and predicted values was larger for municipalities where few measurements were available. This meant that uncertainties in measurement-based exposure assessments for a given area are dependent on the number of available measurements. For areas with fewer meas-

urements, uncertainties are larger because the measured houses may not have been chosen representatively. Uncertainties in the model-based approach depend on the underlying regression model. We detected underestimations of peak radon values, resulting possibly mainly from not considering relevant predictors in the radon prediction model. However, we found that the model-based approach allows predicting radon levels at specific sites and for specific subgroups such as different age-groups. Hence, it is possible with our radon prediction model to identify buildings with a high radon risk. Such estimations however are difficult with the measurement-based approach unless a high proportion of houses are measured or the measurement sites have been randomly selected. The advantage of the measurement-based approach is its simplicity, which is sufficient for assessing exposure distribution in a population.

***Objective 3:*** domestic radon exposure and the risk of childhood cancer

Based on the radon prediction model, described in Article 1, arithmetic mean radon concentration was estimated to be 85.7 Bq/m³ (range: 6.9-337.2 Bq/m³) for childhood cancer cases and 85.9 Bq/m³ (range: 0.7-490.1 Bq/m³) for the rest of the study population. Arithmetic mean radon concentrations were estimated to be lowest (83.7 Bq/m³) for ALL cases and highest for CNS tumour cases (88.9 Bq/m³).

The finding from the analyses did not show evidence that domestic radon exposure is associated with childhood cancers despite relatively high radon levels in Switzerland. Compared with children exposed to a radon concentration below the median (< 77.7 Bq/m³), hazard ratios (HR) for children with exposure ≥ 90th percentile (≥ 139.9 Bq/m³) were 0.93 (95% confidence interval (CI): 0.74, 1.16) for all cancers, 0.95 (95% CI: 0.63, 1.43) for all leukaemias, 0.90 (95% CI: 0.56, 1.43) for acute lymphoblastic leukaemia (ALL ) and 1.05 (95% CI: 0.68, 1.61) for CNS tumours.

The results were found to be consistent with dose estimations to different organs. Estimated doses to other organs than to the lung were found to be too weak to noticeably increase cancer risks.

**Aim 2:** to assess whether exposure to background gamma radiation is associated with childhood cancers

The findings from the main analysis did not indicate an association between background gamma radiation and childhood cancer. Subgroup analysis, considering the effect of residential mobility indicated an association between background gamma radiation exposure and childhood leukaemia (including ALL) for children who lived at the same address between 1995 and 2000. The association between outdoor gamma radiation and all leukaemias, including ALL was enhanced for this group of children and the results were significant for all leukaemias and for the highest exposure group in terms of ALL. In contrast, no association between background gamma radiation childhood leukaemia (including ALL) was found when considering the group of children who moved between 1995 and 2000. On the other hand, hazard ratios were elevated for CNS tumours when considering the group of children who moved between 1995 and 2000. In this case, a significant result was seen for the medium exposure category.

**Aim 3:** to assess whether exposure to radiofrequency electromagnetic fields from broadcast transmitters is associated with childhood cancer

Fifty one per cent of all children who were considered for the time-to-event analysis on RF-EMF exposure to broadcast transmitters and childhood cancer lived within the modelled area at the time of census 2000. Arithmetic mean exposure in the whole study sample within the modelled area was 0.14 V/m where the maximum value was 9.77 V/m.

We found no association between RF-EMF from broadcasting and childhood leukaemia but elevated CNS tumour risks in some of the analyses. In the time-to-event analysis, hazard ratios (HR) for the highest exposure category (≥ 0.2 V/m) compared to the reference group (<0.05 V/m) were 1.03 (95% CI 0.74, 1.43) for all cancers, 0.55 (95%-CI: 0.26, 1.19) for leukaemia, 0.61 (95%-CI: 0.27, 1.41) for ALL and 1.71 (95% CI 0.99, 2.94) for CNS tumours. Increased CNS tumour risks were also indicated in the linear exposure response analyses where the positive correlation with CNS tumours reached sta-

tistical significance for all types of transmitters. However, the Poisson analysis indicated increased CNS tumour risks in the data before 1995 (HR: 1.60, 95%-CI: 0.98, 2.61) but not thereafter (HR: 0.75, 95%-CI: 0.45, 1.23). On the other hand, the Poisson analysis did not indicated increased CNS tumour risks for the entire period between 1985 and 2008.

# 7 General discussion

## 7.1. Methodological aspects

### *7.1.1 Radon exposure assessment*

Based on the evidence for an association between residential radon exposure and lung cancer in adults, the national radon program in Switzerland aims to reduce radon exposure of the Swiss population (127). To meet this aim, it has been recognised that knowledge on radon in inhabited rooms needs to be better understood (127). A good exposure assessment is therefore essential, which involves refinement and application of appropriate methodologies. This also applies to epidemiological studies on radon.

In Switzerland, radon measurements of almost 7% of all buildings are currently available. The national radon action plan (40) also states that additional measurements are necessary in order to better evaluate the radon risk of the Swiss population and to identify buildings with a high radon risk. The Swiss government set the threshold value where constructional actions are mandatory to 1,000 Bq/m³ and the legal action level where constructional actions are recommended to 400 Bq/m³ (127). Due to the epidemiological findings on indoor radon concentrations and lung cancer the World Health Organisation (WHO) set corresponding values to 300 Bq/m³ and 100 Bq/m³ respectively (8). The Swiss government aims therefore to identify buildings where radon values exceed the threshold level of 300 Bq/m³. Measurements have been the principal method for assessing residential radon concentrations in the past, seen as the gold standard to determine radon levels in a specific building. It is argued that the diffusion process from radon gas from soils into buildings would be too complex to be captured with factors such as building characteristics (1), as it is done with radon prediction models. Second, factors such as daily room ventilation, type of fundament, degree of pressure under a particular building, sealing between the houses and the ground probably explain a substantial portion of the variation of radon levels between different households. Data on such factors, however, are seldom collected and therefore it is not possible to consider such factors in a radon prediction model. Underesti-

mated peak values which were detected when predicting radon concentrations for all Swiss households were mainly explained with the absence of such relevant predictors in the prediction model (92). Finally, regression to the mean is a further explanation for lower predicted values than measured values. That means that for a measured value, its predicted value is always closer to the mean than the measured value itself (128). Therefore, public authorities might be more interested in measured values than predicted values that allow a better identification of households in high risk buildings than predictions.

However, there are several motivations for the use of a prediction model rather than measurement for assessing domestic radon exposure. First, it is clearly recognized in the national radon action plan that it would be impossible to carry out measurements in all living rooms in Switzerland due to the cost alone. For this reason model based predictions, which enable assessment of radon exposure for each household, are an attractive alternative. This thesis thus fills an important gap by providing radon exposure estimates for each household and individual in Switzerland without the need of additional measurements. Supported by the existing large number of radon measurements, available all over Switzerland, a radon prediction model was developed for exposure assessment. This model could then be applied at households where information about the prediction factors was available. Second, exposure assessments, based on measurements might be limited by the non-representative selection of measurement sites, as described in Article 2. According to the national radon action plan in Switzerland, measurements to date focused on evaluating levels in high risk buildings (i.e. older detached houses potentially requiring remedial action) rather than specifically for epidemiological investigations of health risks to the general population. The work conducted in this thesis confirmed the non-representative selection of households leading to biased estimated radon values in inhabited rooms. In contrast, the model-based approach applied for each individual household, considered the population distribution and thus is less likely to overestimate the true radon concentration.

These arguments highlight the important contribution of our model-based assessment to the study of residential radon exposure. Despite its limitation, also mentioned in the publications on the radon prediction model and the comparison with the measurement-based exposure assessment, the model-based approach can help identify buildings with a high radon risk in a systematic way by allowing the estimation of radon exposure distribution, e.g. the estimation of the percentage of households in a specific area, exceeding the reference value of 100 Bq/m³. The prediction model is therefore suitable for identifying households with high and low radon concentration and to determine average radon exposure of the Swiss population. This is important for epidemiological studies on health effects of domestic radon exposure.

To summarize, the model-based approach helps fulfil the aim of the national radon action plan by expanding knowledge on radon exposure in inhabited rooms and identifying high risk buildings were remedial actions might be necessary.

### *7.1.2 Study results in the context of exposure assessment and study design*

A major limitation of past studies exploring environmental risk factors in relation to cancers in children was the selected study design and poor exposure assessment. This resulted in biased and inconsistent exposure-response relationships for childhood cancers. As reported, ecological studies are vulnerable to ecological fallacy. Case-control studies are often faced with recall and selection bias. It became further evident that biases in measurement-based exposure assessments can be introduced due to insufficient numbers of available measurements for a given area or by the selection of measurement sites in a non-representative way. Our studies on ionizing and non-ionizing radiation and childhood cancer had the advantage that selection bias was minimized because no direct contact with study participants was necessary. In terms of domestic radon exposure and childhood cancer for example, only two recently published case-control studies from the United Kingdom (73) and Denmark (77) were based on data from cancer registries and modelled radon values. Despite that model-based exposure assessments will introduce exposure uncertainties, we are convinced that exposure assessment based on predictions for each individual household and data from cancer registries are more reliable than measurements since they overcome

the limitations of measurement-based and interview-based studies. We further did not have to rely on exposure proxies such as distance to the next broadcast transmitter. Our studies also had strength that it was tested for numerous potential confounding factors. The British case-control study (73) on domestic radon exposure, gamma radiation and childhood cancer tested for socio-economic status as potential confounder only, as no information on other potential confounders was available. The Danish case-control study (77) on domestic radon exposure tested for birth order, mother's age, traffic density and electromagnetic fields from high voltage facilities as potential confounders. In this context, it is important to note that modelled values for PM10, $NO_2$ and benzene pollution were considered as potential confounders in our study. We did not use proxies for these atmospheric pollutants such as traffic density or gasoline consumption as such proxies might lead to biased exposure-response relationships and to residual confounding if they are considered as confounders (6).

To our knowledge, the analyses for this thesis in the field of ionizing and non-ionizing radiation and childhood cancer were the first ones where prospective census-based cohort study designs were used. The cohort study design has several advantages compared to case-control studies. First, it enables determination of the temporal sequence of cancer incidence. Cohort studies are further regarded as being less susceptible to recall bias in terms of exposure, as exposure precedes the outcome of interest. But a registry based case-control design could have likewise been applied for the studies in this thesis. Case-control studies based on cancer registries and modelled radon values also do not suffer from participation and recall bias. Therefore, they are likewise applicable for the research questions of this thesis. In terms of modelled radon values for example, registry based case-control studies are faced with the same limitations of their prediction models and thus with the same uncertainties as faced here. Case-control studies also allow the consideration of various potential confounders.

Based on this discussion, the lesson that can be learned is that studies, based on registries and modelled exposure levels while considering potential confounding factors would be preferable for the evaluation of the carcinogenic effects of other environmental factors.

It should be finally pointed out that past studies on domestic radon exposure seldom considered other health outcomes than childhood leukaemia. The same applies to past studies on RF-EMF exposure or on gamma radiation and childhood cancer. Only a few ecological and case-control studies considered CNS tumours in children as health outcome. As CNS tumours belong to the most common malignancies in children, this thesis further fills this important gap in the knowledge.

## 7.2 Domestic radon exposure and childhood cancer: study results in the context of dose estimations

### *7.2.1 General aspects*

Various estimations of equivalent doses from radon and its decay products to different body organs were carried out in the past (46, 60, 65). The dose estimations differed between pre-school children (1 year old children), school children (10 year old children) and adults.

When looking at the doses to different organs at a radon concentration of 100 Bq/m³, i.e. the radon concentration where remedial actions are recommended according to the WHO, one notes the highest doses for organs of intake, i.e. respiratory tract in case of inhalation (Table 5). Contribution of radon gas and its decay products to dose to other organs such as the red bone marrow or the brain are much smaller. For some organs in particular, the dose from radon gas itself rather than from its decay products are thought to be more relevant. The reason is that radon is highly soluble in organs with high fat content, being sixteen times higher than in tissues without fat (88). Except for in one-year olds, the red bone marrow has a high fat content (estimated to be 40% fat for adults) (88). In this context, radon gas itself thus plays a more important role in terms of dose. Organ-specific annual equivalent doses of radon gas for the red bone marrow are estimated to be 0.33 mSv for an adult, 0.29 mSv for a ten year old child and 0.13 mSv for a one year old child (60). Due to the high fat content of the red bone marrow, doses from the radon gas were supposed to be high enough to increase the risk of developing leukaemia (88). However, doses from radon gas for the red bone marrow are still smaller than those for the lung (60). This is due to the fact that

most of the inhaled gas is breathed out again (60). The observed lack of an association between domestic radon exposure and childhood leukaemia or CNS tumours in our study strengthens the assumption that doses to organs other than the lung would be too weak to increase cancer risks, whereas there are no differences regarding doses from radon gas itself or from its decay products.

**Table 5: Annual dose estimations (mSv) of radon gas and its decay products for selected organs at a radon concentration of 100 Bq/m³, based on estimations for Britain (60)**

| | 1 year old | 10 years old | adult |
|---|---|---|---|
| Lung | 19.6 | 21.1 | 18.6 |
| Brain | 0.19 | 0.14 | 0.11 |
| Stomach | 0.23 | 0.17 | 0.13 |
| Colon | 0.20 | 0.15 | 0.11 |
| Liver | 0.44 | 0.34 | 0.26 |
| Breast | 0.21 | 0.16 | 0.29 |
| Kidney | 3.98 | 3.37 | 2.63 |
| Gonads | 0.19 | 0.14 | 0.1 |
| Red bone marrow | 0.43 | 0.52 | 0.47 |

### *7.2.2 Dose estimations: relevance of in utero exposure*

The development of childhood leukaemia, in most cases, is thought to be initiated in utero (14) and doses from natural background radiation received in utero may play an important role. Recently, the percentage of leukaemia cases, attributable to natural background radiation was estimated to be 19.2% (using UNSCEAR risk models) and 14.6% (using BEIR VII risk models) when red bone marrow doses received in utero

were considered. When excluding these doses received in utero from the respective risk models the percentage of leukaemia cases attributable to natural background radiation dropped to 3.7% (UNSCEAR risk model) and to 2.9% (BEIR VII risk model) (3). Therefore, consideration of maternal exposure to domestic radon during pregnancy could have been interesting to complete our data for the exposure of the children at the time of census 2000. However, the formation of blood cells in the bone marrow occurs only during the last months of pregnancy (16) whereas during mid-gestation hematopoiesis is localised in the liver (16). Therefore, it is an open question which one of the dose –the dose received by the liver or the dose received by the bone marrow- would be more relevant for the induction of leukaemia.

## 7.3 Low dose ionizing radiation and childhood cancer risk: evaluation of a possible relationship

This thesis strengthens the hypothesis that low dose ionizing gamma radiation might be relevant in terms of childhood leukaemia. The findings indicate an association between background gamma radiation exposure and childhood leukaemia (including ALL) for children who lived at the same address between 1995 and 2000. These results probably indicate that the same gamma radiation dose to the red bone marrow over a longer time period is necessary for gamma radiation to lead to childhood leukaemia.

The elevated hazard ratios for leukaemias for children who lived at the same address between 1995 and 2000, are comparable with the much larger, registry based case-control study from the United Kingdom (73). The British study considered cumulative exposure to gamma rays over a certain time period and in terms of gamma ray doses, county district means were considered for each residence. This study comprised 27,447 cases and 36,793 controls also found an elevated, significant excess relative risk for childhood leukaemia with increasing dose of natural gamma radiation while considering cumulative exposure to gamma rays. Absorbed gamma ray dose between address at birth and address at diagnosis was considered, given that the address at birth was the same as the address of diagnosis for 50% of the cancer cases. Second, 83% of the cases resided in the same county district between time of exposure and

time of diagnosis and thus had the same mean absorbed gamma dose rate over this time period.

Our results on background gamma radiation and childhood leukaemias, for children who lived at the same address between 1995 and 2000, seem to be consistent with dose estimations for different organs and tissues. These dose estimations suggest that doses to the red bone marrow from gamma radiation are more important than from alpha radiation (46). The result for childhood leukaemia could also be explained with the higher sensitivity of the red bone marrow than of other body organs to ionizing radiation (Table 2).

In contrast, the elevated hazard ratios for CNS tumours for the group of children who moved between 1995 and 2000 are neither intuitive nor consistent with the sensitivity to ionizing radiation of different tissues. The brain was found to be much less sensitive to ionizing radiation than other organs (Table 2). In addition, the larger British case-control study (73) found less elevated risks for CNS tumours than for leukaemias and reported a non-significant association between gamma radiation and CNS tumours. They drew the conclusion that gamma radiation would play a less important role for other childhood cancers than for leukaemia. In the light of present results and the literature, there is currently little evidence for a causal relationship between background gamma radiation and CNS tumour risk in children.

To the authors' knowledge, this is the first prospective cohort study on natural gamma radiation and childhood cancers. As for the analysis on domestic radon exposure and that on broadcast transmitters, the strength of this analysis is its nationwide coverage which minimizes a potential risk of selection bias. Further, exposure assessment was based on digital maps with outdoor gamma ray dose rates. Therefore, incomplete participation rate, with which a previous case-control study (71) was faced, was not an issue in this study. Compared to ecological studies and two previous case-control studies (70, 71), a large selection of potential confounding factors was available for which the models could be adjusted for. So far, only the British, registry-based case control study (73) had similar methodological features, i.e. a small likelihood for selec-

tion bias due to complete control selection from population registries without needing consent for participation. This study also considered confounding factors.

Our study also has limitations. First, we could not consider the effect of moving in the main analysis because it was only possible to consider exposure at the time of census 2000 but not for earlier living places. Addresses prior to 2000 were only available for cancer cases. The same was true for the subgroup of children from whom we knew had moved between 1995 and 2000. This could have resulted in non-differential exposure misclassification and thus partially explain lack of an association in the main analysis or the subgroup analysis of children who had moved. Non-differential exposure misclassification is also of concern with respect to the low resolution of the Swiss radiation map. This digital map has a grid cell resolution of 2km only. This could have resulted in an attenuation of the dose-response associations if there were true associations.

In their conclusion, Kendall et al. (2012) (73) point out that studies from other countries with higher and more variable natural background radiation levels than in the United Kingdom would be needed. In the control group of the British study, arithmetic mean of the absorbed gamma-ray dose rates from terrestrial and cosmic radiation was 94.7 nGy/h, ranging from 38.1 nGy/h to 159.7 nGy/h (73). For the study population considered for this thesis, a higher arithmetic mean (109 nGy/h) and larger exposure contrast (range: 55 to 383 nSv/h) for absorbed gamma-ray dose rates were estimated. Despite the lower number of cases, this thesis confirms the result on ionizing gamma radiation and childhood leukaemia that was found in the British study and strengthens the evidence for a relationship between low-dose ionizing radiation and childhood leukaemia.

## 7.4 Public health relevance

Although evidence for an association with childhood cancer was not found, domestic radon exposure is of public health relevance especially with regard to lung cancer in adults. A relationship between domestic radon exposure and lung cancer was derived from animal and laboratory studies (63) and strong evidence has been provided from

recently published pooled analyses (74, 75). Radon is seen as the leading cause of lung cancer among never smokers (129) and the second most important cause for lung cancer after smoking (130). Radon is of particular public health relevance, as exposition in ubiquitous. It was estimated that radon causes more than 100,000 lung cancer deaths worldwide each year and that this figure is higher than that from environmental tobacco smoke exposure (130). Lung cancer is the most common fatal cancer disease among men and a rising number of deaths among women are attributable to lung cancer (127). More than 3,600 persons are diagnosed with lung cancer every year in Switzerland (127). Treatment of this type of tumour remains difficult and survival rate five years after diagnosis was estimated to be 10% (127).

The predictions from our model confirm that average domestic radon concentrations are relatively high in Switzerland due to the geology. Areas with high domestic radon values are mainly found in the Alps and the Jurassic region. Our predictions indicated that the legal action level, as defined by the WHO is frequently exceeded in the Jurassic and the Alpine regions. Given these high radon values in many regions in Switzerland and the availability of predictions for each individual from our exposure model, it was of interest for me to further evaluate the public health relevance of domestic radon exposure. For this purpose, I estimated the percentage of lung cancer deaths that can be attributed to domestic radon exposure. For this assessment, I used the predictions from our exposure model and risk estimates from the past two pooled analyses (74, 75), mentioned above. Both these studies provide excess relative risks/odds ratios per 100 Bq/m³. I further considered the permanent population in Switzerland in 2010 and the number of deaths from lung cancer that were also available for 2010. I also considered a hypothetical scenario with a realistic, non-zero baseline radon concentration. For this purpose, I oriented myself on the past health impact assessment, described in article 2, where lung cancer deaths, attributable to domestic radon exposure were estimated (122). These authors considered the outdoor radon concentration as baseline radon concentration while using a radon value of 10 Bq/m³ for outdoor radon concentrations in Switzerland. Table 6 presents the number of lung cancer deaths, attributable to domestic radon exposure. Based on such a calculation, I estimated that between 8 to 12% of all lung cancer deaths can be estimated to be due to

domestic radon exposure. When neglecting the uncertainties from the European pooled study (74), this figure fell to 6%. The other health impact assessment (122) estimated this figure to be 8.3%, based on an estimated average indoor radon concentration of 78 Bq/m³.

**Table 6: number of lung cancer deaths, attributable to domestic radon exposure**

| Permanent resident population 2010 (> 20 years (n) (131) | Lung cancer deaths 2010 (> 14 years) (n) (132) | Domestic radon exposure[1] | RR/OR (95%-CI) per 100 Bq/m³ | attributable deaths (95%-CI) (n)[2] |
|---|---|---|---|---|
| 6,227,699 | 3,143 | 84 Bq/m³ | 1.16 (1.05, 1.31)[3] (74) | 372 (116, 721) |
| 6,227,699 | 3,143 | 84 Bq/m³ | 1.08 (1.03, 1.16)[4] (74) | 186 (70, 367) |
| 6,227,699 | 3,143 | 84 Bq/m³ | 1.11 (1.00, 1.28) (75) | 245 (0, 623) |

[1] domestic radon exposure, estimated for all individuals, aged > 15 years at the date of census 2000

[2] the number of lung cancer deaths, attributable to domestic radon exposure were calculated as following:

ERR/EOR=RR/OR-1

D = $P_0$ * ERR per 100,000 person-years, where $P_0$ = number of lung cancer deaths per 100,000 inhabitants

C = (domestic radon exposure – baseline exposure)/100 Bq/m³

➔ number of attributable lung cancer deaths: n= P*D*C, where: P = permanent resident population

[3] RR from lung cancer from the European pooled study, additionally considering measurement uncertainties

[4] RR from lung cancer from the European pooled study, not considering measurement uncertainties

With respect to the lung cancer risks and according to the model-based predictions and the WHO guidelines, remedial actions are recommended for almost a third of all Swiss households. The Federal Office of Public Health (133) aims at focusing on long-lasting sealing of foundations in all Swiss buildings. Remedial actions are also justified, given that around 10% of all lung cancer deaths in Switzerland are due to domestic radon exposure. Nevertheless, 60% of the Swiss population have never heard from radon and thus do not know about the risks of radon on health (127). A national campaign which promotes public knowledge on domestic radon exposure as a lung cancer risk will also be necessary.

The findings from the analyses on gamma radiation in childhood cancer indicate that gamma radiation is of public health relevance as well, especially when children are exposed to the same gamma radiation dose over a longer time period. Remedial actions are likewise necessary in order to reduce exposure from gamma radiation. Radionuclides that are responsible for terrestrial radiation are also found in building materials consisting of granitic and metamorphic stones. Therefore, a prevention strategy could consist in avoiding using building material with high uranium content.

# 8 Outlook

Our cohort study contributes to a better understanding on ionizing and non-ionizing radiation and childhood cancer. Several suggestions in terms of future research, however, are provided below.

Low statistical power is an important issue in many epidemiological studies of diffuse environmental pollution, in particular for low-dose ionizing radiation where a small radiation dose correlates with a small excess risk (134). Assuming excess risk being proportional to gamma radiation dose, it was estimated that a sample size of 50,000 persons would be needed for 100mSv dose and a sample size of 5 million for a 10 mSv dose (134, 135). The same probably also applies to domestic radon exposure. In terms of low dose ionizing radiation and childhood cancer, a large study with a high exposure contrast would be needed to detect a potential. So far, many studies on radon or gamma radiation and childhood leukaemia suffered from low power related to low sample size and low exposure contrast. Our studies on domestic radon exposure and background gamma radiation included fewer cases than two recently published large register based case-control studies (73, 77) which were still considered to be low powered (73). This means that we had even less power to detect a significant association. Our results, however, were consistent with the British study (73). A high exposure contrast is considered more important than a large sample (72). Thus, in terms of statistical power, the large differences in exposure levels of the study population in the analyses on domestic radon exposure and the higher exposure contrast in terms of gamma radiation in Switzerland than in the UK may at least partly compensate for the lower number of cases. However, the non-elevated and not significant hazard ratios for the main analyses on gamma radiation and childhood cancer could additionally be due to insufficient number of cancer cases besides the non-differential exposure misclassification, mentioned in chapter 7.3. In order to rule out small effects of low dose ionizing radiation on childhood leukaemia or CNS tumours, a transnational census-based cohort study with a long follow-up period, relaying on model-based exposure assessment and data from cancer registries would be needed. Besides a large sample size, such a study would also offer large exposure contrasts that in turn would increase

the power of the study. However, such an effort would also require that cancer registries are build up consistently across the different countries with the same criteria and the same registration completeness.

Although not explored here, domestic radon exposure might also be of public health relevance due to a possible association with skin cancer. Although the association with skin cancer is still insufficiently understood, the literature indicates that radon decay products might decay on the skin and be responsible for alpha radiation of the outer layer (60). This can be especially problematic for body parts with thin skin such as the face. Alpha particles might more easily reach the susceptible cells thus causing cancer (60). Recently, a study on radon and skin cancer in the Southwest of England (136) was published and found an association but the study has its limitation in its ecological study design. Hence, another task should be to carry out cohort studies or registered and model based case-control studies on domestic radon exposure and skin cancer, to better understand the exposure of the susceptible cells in the dermis to radiation from alpha particles due to radon decay products.

So far, most analyses on ionizing radiation, including domestic radon exposure, investigated its effects on cancer. However, in terms of public health relevance, it would also be important to understand possible associations between ionizing radiation and other diseases. Diseases such as circulatory diseases or neurological disorders have rarely been examined and biological mechanisms by which low dose ionizing radiation causes circulatory diseases is not yet well understood (137), to date with circulatory disease studies largely restricted to Uranium miners (138-143). A recent systematic review found twenty-six studies on low dose ionizing radiation from diagnostic or occupational exposure (radiologists, radiation workers, Uranium miners) and circulatory diseases, concluded that the evidence for low dose ionizing radiation increasing the risk of circulatory diseases was lacking (144). A recent meta-analysis found an association between occupational exposure and circulatory diseases, though it did not consider various confounding factors (137). The much lower radon doses measured in other organs than the lung, such as the arteries, suggest that domestic radon exposure likely poses no risk for circulatory diseases. Annual equivalent dose at radon con-

centration of 100 mSv to the intima, i.e. the innermost layer of the artery, ranges from 0.06 to 0.08 mSv for healthy persons and rises up to 0.17 mSv for elderly persons with severe stenosis (88). Thus far, the potential relevance of different tissues in the progression of low-dose ionizing radiation effects towards circulatory disease is still unclear (137). Given that this research has focused on occupational exposures, a future task will be to carry out studies on low dose ionizing radiation and circulatory diseases, which consider the general population, potential confounding factors and contribute to a better understanding of the biological mechanisms. Despite the lower doses reported to the intima than to the lung, it would also be of interest to investigate if doses from radon to the intima might still be high enough to cause for circulatory diseases.

An important Hill criteria is that the presence or absence of an association between an environmental factor and a disease should biologically plausible (36). Despite the available dose estimations (46, 60, 65) and epidemiological studies conducted to date, there is no direct human evidence so far that low dose ionizing radiation causes childhood cancer (145). Dose estimations which were used for a plausibility assessment of the results from the epidemiological analyses are based on simplifying assumptions. Radiation and tissue weighting factors, used for the estimation of equivalent and effective doses to organs and tissues do not consider individual characteristics (16). Radiation weighting factors do not consider difference in the biological effectiveness of different alpha particles (16). Fortunately, integration of epidemiological and biological research is currently being promoted for this purpose by the DoReMi (Low Dose Research towards Multidisciplinary Integration) network. The aim of DoReMi is to undertake large-scale molecular epidemiological studies that consider biomarkers and scientific experiments on animals and bacteria (145). Due to the required collection of biological samples, therefore, a prospective cohort study that would allow the collection immediately after the exposure would be most appropriate. In a case-control study, it is not possible to simultaneously collect biological samples and assess exposures, given that the interest in this study design is in past exposures. In terms of biomarkers, cohort studies would require direct contact with persons in order to collect

biological samples (145). Carrying out such a study based on cancer cases from registries is not possible.

In contrast to domestic radon exposure or exposure to background gamma radiation, statements on a possible public health relevance concerning non-ionizing radiation from broadcast transmitters are not yet possible. The analyses indicated no association between RF-EMF from broadcasting and childhood leukaemia. However, increased CNS tumour risks were found in some of the analyses. These results were less clear, as they contradict past case-control studies on RF-EMF exposure from broadcast transmitters (114, 115) or mobile phone base stations (117) and central nervous system tumours. In particular, they further contradict animal, in-vivo and in-vitro studies as they did not find evidence for genotoxic effects such as DNA mutations. Finally, one would also expect increased risk from use of wireless phones, which lead to substantially higher exposure to the head. However, such an association was also not observed in previous studies. It is suggested that a new prospective cohort or case-control study should be carried out in another country than Switzerland, before statements on possible public health relevance of RF-EMF exposure and CNS tumours in children can be made. This study should aim at investigating whether there is an association between RF-EMF from broadcast transmitters and CNS tumours in children. Analogous to our study, such a study should be based on census data and cancer cases from registries and modeled field strengths. This would allow seeing whether results from such a study are consistent with the findings from our study. Ideally, such a study should consider the time periods before 1995 and after 1995 separately as well accounting for the larger contribution of broadcast transmitters to the overall RF-EMF exposure before the advent of mobile and cordless phones.

Finally, it would have of interest for me to compare radon levels of Switzerland with those from other countries. This would have allowed me to compare the estimated number of lung cancer deaths from Switzerland with those from other countries and to demonstrate the public health importance of residential radon exposure in other countries as well. Currently, such a task is very difficult. An overview of radon surveys in Europe (146) as well as a recent publication (147), presenting the status of the Euro-

pean radon map, clearly state that many countries have only few measurements available and second, the measurements strategies differ between different countries. One of these authors (147) confirmed me in an e-mail (23.02.2012) these different measurement strategies (i.e. some countries did not apply seasonal corrections, differences in sampling time (ranging from few hours to more than a year)) and stated that the measurements for the publications, mentioned above were carried out on ground floors. Measurements from ground floors however are not representative for the population distribution since many households are situated on upper floors, especially in larger cities. Hence, comparable measurement strategies as well as representative exposure assessments in other countries that could be based on predictions form exposure models will be necessary, before comparisons of residential radon exposure between different countries can be made.

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## Curriculum vitae

| | |
|---|---|
| Name | Dimitri Daniel Hauri |
| Date of birth | 26.09.1972 |
| Nationality | Swiss |

**Education**

| | |
|---|---|
| 1993 –2000 | Geography Study, University of Zurich, Switzerland diploma degree, subsidiary subjects: Geology, mathematics, anthropology, palaeontology. Master Thesis: „The implementation of the concept on sustainable development within the European Union with reference to biodiversity – illustrated with the case sample of the Wadden Sea" |
| 1999 | Internship: national park „Schleswig-Holstein Wadden Sea", Germany, ornithological observations, resting bird counts, guidance of tourists |
| 1995 –1996 | Geography Study, University of Sheffield, United Kingdom, ERASMUS/SOCRATES exchange-program |
| 1992 | High-school Graduation, Matura Typ B (latin) |

**Further training:**

| | |
|---|---|
| 2008-2012 | Summer School, International Agency for Research in Cancer (IARC): introduction to cancer epidemiology |
| | Various trainings in the field of Geographical Information Systems (GIS), statistics, epidemiology and Public Health within the PhD-Program SSPHPLUS and within courses, held at the University of Basel |

| | |
|---|---|
| 2003 – 2005 | Postgraduate Course in applied Statistics, ETH Zurich, Switzerland. Project work: „preferences for landscapes: evaluation of a survey" |

**Working experience**

| | |
|---|---|
| 2008 - 2010 | Research Scientist, Institute of Social and Preventive Medicine (ISPM), University of Bern, Swiss Tropical and Public Health Institute, Basel. Research project: "Health risk assessment from passive smoke exposure in public buildings" |
| 2007 - 2008 | Research Scientist, Horten Centre, University Hospital of Zurich. Statistical analysis of clinical data |
| 2004 –2007 | Research Scientist, subunit Social Sciences in Landscape Research Swiss Federal Institute for Forest, Snow and Landscape Research, Birmensdorf, Switzerland. Analysis of socio-economic data, participation on the preparation and carrying-out of telephonic surveys, independent evaluation of the data, writing of reports within the research project „transalpine freight traffic's impact on people's quality of life". |
| 2001 –2004 | Project Support, Lead Consultants, Zurich, Switzerland. Acquisition, processing and evaluation of project data within the technological high school planning |
| 2001 | Assistant / Research Scientist, Institute for Transport Planning and Systems (IVT), ETH Zurich, Switzerland. Enquiries of statistical information, building up of databases, representing of spatial information by ArcInfo/ArcView |

**List of Publications**

Hauri DD, Huss A, Zimmermann F, Kuehni CE, Röösli M (2013) Prediction of residential radon exposure of the whole Swiss population: comparison of model-based predictions with measurement-based predictions, Indoor Air, Epub 2013/03/08

Coulibaly JT, Fürst T, Silué KD, Knopp S, Hauri D, Ouattara M, Utzinger J, N'Goran EK (2012) Intestinal parasitic infections in schoolchildren in different settings of Côte d'Ivoire: effect of diagnostic approach and implications for control. Parasit Vectors 5, 135-.

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Hauri D, Lieb CM, Rajkumar S, Kooijman C, Sommer HL, Röösli M (2011) Direct health costs of environmental tobacco smoke exposure and indirect health benefits due to smoking ban introduction. Eur J Public Health 21, 316-322

Vonlanthen R, Slankamenac K, Breitenstein S, Puhan MA, Muller MK, Hahnloser D, Hauri D, Graf R, Clavien PA. (2011): The impact of complications on costs of major surgical procedures: a cost analysis of 1200 patient, Ann Surg. 2011 Dec;254(6):907-13.

Franzen D, Rupprecht C, Hauri D, Bleisch JA, Staubli M, Puhan MA. (2010): Predicting outcomes in critically ill patients with acute kidney injury undergoing intermittent hemodialysis - A retrospective cohort analysis, Int J Artif Organs, 33(1):15-21

Hauri D, Lieb C, Kooijman C, Wenk S, Van Nieuwkoop R, Sommer H, Röösli M Gesundheitskosten des Passivrauchens in der Schweiz. (2009).

Schmidlin PR, Hauri D, Krähenmann MA, Puhan MA, Attin T. (2009): Residual pockets after periodontal regenerative procedures--clinical relevance and interpretation of meta-analyses data, Schweiz Monatsschr Zahnmed., 119(3):224-31

Winter, U. D. Hauri, S. Huber, J. Jenewein, U. Schnyder, B. Kraemer (2009): The Psychological Outcome of Religious Coping with Stressful Life Events in a Swiss Sample of Church Attendees, Psychotherapy and Psychosomatics, 78:240–244

Hauri D, Schmidlin PR, Puhan MA. (2008): Development of an easily interpretable presentation format for meta-analyses in periodontal surgery, Evidence-based dentistry, 9(3):89-90

Bauer, N.; Hauri, D.; Hunziker, M. (2008): Landschaftsbezogene Lebensqualität in Transit- und Referenzregionen. In: Buchecker, M; Frick, J; Tobias, S. (eds) Gesellschaftliche Ansprüche an den Lebens- und Erholungsraum. Eine praxisorientierte Synthese der Erkenntnisse aus zwei Forschungsprogrammen. Birmensdorf, Eidg. Forschungsanstalt WSL. 17-20

Valkova, K., K. Schulthess, D. Hauri, L. M. Bachmann, J. Steurer, A. Seidenberg (2008): Hepatitis C infections in Opioid-dependent Patients (HepCOP2): What determines the state of care in the canton of Zurich?, http://www.seidenberg.ch/media/HepCOP2a_SGG_082008.pdf

Hauri D. (2007): Medical geography, Schweiz Rundsch Med Prax, 96(42),1627-30

Hauri, D.; N. Bauer (2006): Transalpine freight traffic's impact on people's quality of life. In: Brebbia, C. A.; V. Dolezel: Urban Transport XII: Urban Transport and the Environment in the 21st Century, WIT Transactions on The Built Environment (Vol. 89), WIT Press, UK, 679–691.

Hauri, D.; Bauer, N. (2006): Eignung von Behavior Settings als Indikator für die Lebensqualität in Transitregionen. [Abstract] In: Lösel, F.; Bender, D. (Hrsg.), 45. Kongress der Deutschen Gesellschaft für Psychologie. Humane Zukunft gestalten. Nürnberg, 17.–21. September 2006. Legerich, Pabst Science Publisher, 126.

Simma, A.; D. Hauri, R. Schlich (2002): Beschreibung einer Datenbank zu den Schweizer Gemeinden, Arbeitsberichte Verkehrs- und Raumplanung (118), Institut für Verkehrsplanung, Transporttechnik, Strassen- und Eisenbahnbau (IVT), ETH Zurich.

Hauri, D. (2001): Analyse von Verkehrsströmen an ausgewählten intermodalen Knotenpunkten in der Schweiz, Arbeitsberichte Verkehrs- und Raumplanung (89), Institut für Verkehrsplanung, Transporttechnik, Strassen- und Eisenbahnbau (IVT), ETH Zurich.

**Conference Contributions**

Hauri, D., Spycher, B., Huss, A., Zimmermann, F., Grotzer, M., von der Weid, N., Kuehni, C.E., Röösli, M. (2012): Domestic radon exposure and risk of childhood cancer: a prospective census-based cohort study from Switzerland, Multidisciplinary European Low Dose Initiative Workshop, Helsinki, Finland, 12.-14. September 2012, poster presentation

Hauri, D., Huss, A., Zimmermann, F., Grotzer, M., von der Weid, N., Kuehni, C.E., Röösli, M. (2012): Radon exposure and childhood cancers, Swiss Public Health Conference, Lausanne, 30.-31. August 2012, oral presentation

Hauri, D., Röösli, M. (2012): An invisible component of the landscape: radon exposure distribution in Switzerland, Internationale Konferenz „Gesundheit und Landschaft: Wirkungen, Potenziale und Strategien", 24. und 25.1.2012, Birmensdorf, Schweiz, oral presentation

Hauri, D., Röösli, M. (2011): Assessment of indoor radon concentrations with a radon prediction model, Conference of the International Society for Environmental Epidemiology (ISEE), Barcelona, 13.-16. September 2011, poster presentation

Hauri, D., Zimmermann, F., Kuehni, C.E., Röösli, M. (2011): Radon exposure of the Swiss population, Swiss Public Health Conference, Basel, 25.-26. August 2011, oral presentation

Hauri, D., Huss, A., Mohler, E., Frei, P., Röösli, M. (2009): Impact of pre- and postnatal exposure to environmental tobacco smoke (ETS) on the sudden infant death syndrome (SIDS), , Conference of the International Society for Environmental Epidemiology (ISEE), Dublin, 25.-29. August 2009, oral presentation

Bauer, N., D. Hauri (2007): Impact of Freight Traffic on the Quality of Life in Alpine Regions, International Conference "Managing Alpine Future", Innsbruck, 15. – 17. October 2007, oral presentation

Bauer, N., D. Hauri (2007): Impact of freight traffic on quality of life and place attachment, Environmental Psychology Conference 2007, University of Bayreuth, 9.-12. September 2007, poster presentation

Hauri, D., N. Bauer (2006): Zusammenhang zwischen der Wohnumfeldzufriedenheit und der Anzahl an Behavior Settings in unterschiedlich verkehrsbelasteten Regionen, Deutsche Gesellschaft für Psychologie, 45. Kongress, University Erlangen-Nürnberg, Nürnberg, 17.–21. September 2006, poster presentation

Hauri, D., N. Bauer (2005): Transalpine freight traffic's impact on people's quality of life, 2th International Conference on Sustainable Development and Planning, 12.–14. September 2005, Bologna (Italy), oral presentation