

1. Summary of the research plan

Background: It is well established from atomic bomb survivors that ionising radiation can cause cancer and that the risk increases linearly (or with slight upward curvature) over a wide range of medium to high doses (>100 mSv). However, there is still a lack of direct epidemiological evidence of effects associated with exposure to low dose radiation (<100 mSv) and current risk assessment in this dose range is based on extrapolation from higher doses. Furthermore, the adjustments needed to assess risks of protracted exposure to low dose rates are unclear. Children are more sensitive to radiation, and medium to high dose ionising radiation is the only environmental risk factor established to date for the two most important cancer types in children: leukaemia and tumours of the central nervous system (CNS). Assessing the effects of low doses remains challenging since the sample size required to detect small increases in risk can only be achieved in large population-based studies. Assessing individual radiation doses received for large samples is difficult. Recent studies of cancer risks associated with paediatric CT-scans and natural background variation, including a Swiss study by the applicants' group, have provided new evidence for effects of low-dose radiation. However, results from studies of background radiation are conflicting. A new study in Switzerland is timely and worthwhile because of a wealth of newly available radiation measurements and cancer incidence data, and the relatively high geographic variation of dose rates due to the country's complex topography and geology.

The project aims to assess the effects of exposure to low dose ionising radiation on cancer risk in children by:

- Improving exposure models of background ionising radiation in Switzerland, including terrestrial gamma radiation, cosmic radiation, and residential radon
- Assessing the association between childhood cancers and background radiation exposure in a nationwide census-based cohort study in Switzerland
- Pooling nationwide data on childhood leukaemia and background radiation from Switzerland, France, Denmark, and Finland to assess effects of age at exposure and cumulative doses to the red bone marrow
- Assessing the dose-response relationship and effects of dose protraction by meta-analysis of data provided by previous studies of low-dose exposure regardless of source
- Calculating the proportion of childhood cancer cases attributable to common sources of radiation in Switzerland

Population and Methods: We will include all children aged 0-15 years from the Swiss National Cohort study and identify cases of childhood cancer through probabilistic record linkage with the Swiss Childhood Cancer Registry. The pooled international analysis will include all children from the respective published studies, extended by the most recent incidence data. Outcomes will include leukaemia with its subgroups acute lymphoid leukaemia (ALL) and acute myeloid leukaemia, and the most frequent cytogenetic subtypes of ALL; lymphoma; CNS tumours with main histological subtypes; and all cancers combined. We will use multivariate geostatistical modelling combining a wide range of airborne, monitoring network, and in situ measurements to estimate exposure to cosmic and terrestrial gamma radiation and residential radon. We will use a questionnaire survey of households with children, obtain radiation measurements at homes and GPS-tracking of children's activities, and extract medical records of reported CT-scans and X-rays to estimate radiation exposure from common sources. We will use Cox proportional hazard models to compare cancer incidence across exposure levels controlling for potential confounders. We will use logistic regression to analyse pooled international case-control data and fit random-effects meta-regression models to standardised risk estimates provided by previous studies for specified doses and mode of delivery (acute, protracted).

Significance: The project will improve our understanding of cancer risks associated with exposure to low-dose radiation at a young age. By providing new original data, maximizing statistical power, and synthesizing all available evidence from previous studies, the project will considerably add to the evidence base from direct epidemiological study of the effects of low-dose exposure. This will allow better quantification of dose-response relationships including effects of dose protraction and age at exposure, as well as estimation of the proportion of childhood cancer cases attributable to ionising radiation. Ultimately, this will provide a better basis for protecting children from avoidable exposure and unnecessary cancer risk, which is particularly important given their heightened vulnerability and the increasingly routine use of radiation in medical diagnostics.