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Review article

Epidemiological studies of natural sources of radiation and childhood cancer: current challenges and future perspectives

Antonella Mazzei-Abba[1], Christophe L. Folly[1], Astrid Coste[1], Richard Wakeford[2], Mark P. Little[3], Ole Raaschou-Nielsen[4], Gerry Kendall[5], Denis Hémon[6], Atte Nikkilä[7], Claudia Spix[8], Anssi Auvinen[9], Ben D. Spycher[1]

[1] Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland
[2] Centre for Occupational and Environmental Health, Institute of Population Health, University of Manchester, UK
[3] Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, USA
[4] Institute of Cancer Epidemiology, Danish Cancer Society, Denmark
[5] Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, UK
[6] Inserm, UMR 1153 Epidemiology and Biostatistics Sorbonne Paris Cité Research Center (CRESS), Epidémiologie des cancers de l'enfant et de l'adolescent Team (EPICEA), Villejuif, F-94807, France; Paris Descartes University, Sorbonne Paris Cité, France
[7] Tampere Center for Child Health Research, Tampere University and Tampere University Hospital, Tampere, Finland
[8] German Childhood Cancer Registry, Institute for Medical Biostatistics, Epidemiology and Informatics, University Medical Center Mainz, Germany
[9] Unit of Health Sciences, Faculty of Social Sciences, Tampere University, Tampere, Finland and STUK - Radiation and Nuclear Safety Authority, Helsinki, Finland

Corresponding author:

Ben D Spycher

Institute of Social and Preventive Medicine (ISPM), University of Bern, Mittelstrasse 43, 3012 Bern, Switzerland.

E-mail: ben.spycher@ispm.unibe.ch

Tel: +41 31 631 33 46

Fax: +41 31 631 35 20

Abbreviations

AL- Acute leukaemia

ALL – Acute lymphoid leukaemia

AML – Acute myeloid leukaemia

ANLL – Acute non-lymphoblastic leukaemia

CNS – Central Nervous System

GB – Great Britain

LSS – Life Span Study

RBM – Red bone marrow

Abstract

Empirical estimation of cancer risks in children associated with low-dose ionizing radiation (<100 mSv) remains a challenge. The main reason is that the required combination of large sample sizes with accurate and comprehensive exposure assessment is difficult to achieve. An international scientific workshop "Childhood cancer and background radiation" organised by the Institute of Social and Preventive Medicine of the University of Bern brought together researchers in this field to evaluate how epidemiological studies on background radiation and childhood cancer can best improve understanding of the effects of low-dose ionising radiation. This review summarises and evaluates the findings of the existing studies in the light of their methodological differences, identifies key limitations and challenges and proposes ways forward. Large childhood cancer registries, such as those in Great Britain, France and Germany, now allow the conducting of studies that should have sufficient statistical power to detect the effects predicted by standard risk models. Nevertheless, larger studies or pooled studies will be needed to investigate disease subgroups. The main challenge is to accurately assess children's individual exposure to radiation from natural sources and from other sources, as well as potentially confounding non-radiation exposures, in such large study populations. For this, the study groups should learn from each other to improve exposure estimation and develop new ways to validate exposure models with personal dosimetry.

Keywords: childhood cancer, background ionising radiation, exposure assessment, record-based study

Introduction

Exposure to high doses of ionizing radiation is known to increase the risk of cancer. Standard risk models based on data from the Life Span Study (LSS) of atomic bomb survivors from Hiroshima and Nagasaki are broadly consistent with a linear/linear-quadratic increase in cancer risk with dose. The excess relative risk (ERR) per gray is modified by sex, age at exposure and time since exposure (1, 2). These variations are pronounced for leukaemia: ERR/Gy is highest after exposure in childhood and reaches a peak some 5 years after exposure (with ERR estimates of about 50 per Sv), declining thereafter (3). Evidence from other studies is also consistent with a higher risk of radiation induced-cancer after exposure during childhood compared to exposure in later life for various cancer types including leukaemia, thyroid, skin, breast and brain cancer (4).

The empirical estimation of excess cancer risks associated with low doses (<100 mGy low-LET radiation) is more difficult due to sample size requirements and the challenge of reliable dosimetry. However, a recent pooled analysis of nine cohort studies with individual dosimetry, including over 260,000 people exposed to low doses during childhood from medical exposure and from the atomic bombs, found evidence of excess risks associated with doses of less than 50 mSv for acute leukaemia (5). The pooled analysis included a large cohort study from the UK that reported that cumulative doses to the red bone marrow (RBM) of about 50 mGy and to the brain of about 60 mGy (2-3 head CT scans) might almost triple the risk of leukaemia and brain tumours (6). A recent nationwide cohort study in the Netherlands included 168,394 children who received one or more CT scans also reported that brain doses of about 20–50 mGy may increase brain tumour risk (7), but no association was observed for leukaemia. However, results from studies of paediatric CT scans need to be interpreted with caution, because of the potential for reverse causation and confounding by indication (8, 9).

Children's heightened susceptibility combined with short latency periods suggest that a meaningful proportion of leukaemia cases in children, and possibly also of central nervous system (CNS) tumours, might be caused by exposure to natural sources of radiation. Indeed, based on standard risk models, studies from Great Britain (GB) and France estimate this proportion to be up to about 20% (10, 11), and in Finland estimates were about 5% (unpublished results), albeit all with large uncertainties.

However, in the LSS, which commenced just over 5 years after the bombings and upon which the standard leukaemia risk models are based, only four cases of leukaemia occurred among survivors with attained age <10 years and their RBM doses were >1 Sv (12). So, caution is required in applying these risk models to children receiving very low annual doses.

Most of the previous ecological studies investigating associations between childhood leukaemia and naturally occurring sources of ionising radiation have found positive associations for radon (13-15) while for gamma radiation and cosmic rays results have been inconsistent (16-22). Early case-control studies of the association between natural sources of radiation and childhood leukaemia were underpowered and have reported mixed results (23-26). The largest of these, the UK Childhood Cancer Study, included over 2000 cases of childhood cancer and reported weak evidence of a negative association between childhood leukaemia and measured radon concentrations (25) but no evidence of an association with measured gamma dose rates (26). However, the proportion of eligible subjects participating in the measurements was low and varied by socio-economic status. Because exposure to these sources is ubiquitous and variation in cumulative doses received by children of similar age are small, large sample sizes are needed to detect the small predicted risk. Given the rarity of childhood cancer, the only way to achieve such sample sizes is by combining data over long periods of systematic cancer registration.

In the last decade, several nationwide record-based studies in Europe, also referred to as registry-based or register-based studies, have investigated associations between childhood cancer and natural sources of radiation including gamma radiation (with or without the cosmic component) (27-31) and domestic radon (27, 30, 32, 33). In contrast to questionnaire- or interview-based studies, record-based studies rely for the most part on comprehensive data compiled systematically for the entire population and do not require any active participation by study members. Exposure prediction models are used to estimate residential exposure to different sources of background radiation.

The Institute of Social and Preventive Medicine of the University of Bern, Switzerland, organized the international scientific workshop “Childhood cancer and background radiation” on June 6th, 2018. The aim of the workshop was to bring together researchers in the field and interested parties from

around the world to discuss how epidemiological studies on background radiation and childhood cancer can improve understanding of the effects of low-dose ionising radiation. The studies presented at the workshop represent all studies that have been conducted based on nationwide registration of childhood cancers.

The purpose of this review is to describe the findings of the existing studies and their methodological differences, identify limitations and challenges, and propose ways forward in this area of research. In the first section, we describe the methods and findings of the studies. The second section highlights the main methodological challenges, providing an inside view from the authors and presenters of the workshop. Finally, we conclude with future perspectives and recommendations for further research.

Review of recent record-based studies

In this section, we briefly summarize each of the record-based studies on natural sources of radiation and childhood cancer in chronological order of their publication (27-33). An overview of the methodological characteristics and findings is presented in **Tables 1 and 2**. More details on methods of assessing exposure to gamma radiation and residential radon are provided in **Tables 3 and 4**. All studies used cancer registries with high completeness to identify cases (31, 34-38).

The first one was a Danish case-control study that examined domestic radon exposure (33). It included 2,400 childhood malignancies (leukaemia, CNS, and malignant lymphoma) diagnosed in 1968-1994. Control children were selected from the Danish Central Population Registry matching on sex and year of birth. Exposure assessment covered all residences in which the child had lived between birth and diagnosis (or equivalent date). Domestic radon exposure was estimated using a regression model developed from measurements in the living rooms of 3,116 Danish dwellings, with predictors including geographical region, soil type, and house characteristics (39). The study found a relative risk (RR) of 1.56 per cumulative exposure of 10^3 Bq/m^3-years (95% confidence interval (CI): 1.05, 2.30) for acute lymphoblastic leukaemia (ALL). No association was observed for childhood acute non-lymphoblastic leukaemia (ANLL) or brain/CNS tumours, with RRs of 0.75 (95% CI: 0.34, 1.62) and 0.92 (95% CI: 0.69, 1.22) per 10^3 Bq/m^3-years, respectively. The exposure model performed relatively

well in predicting radon concentrations in a test sample of 758 independent measurements (coefficient of determination $R^2 = 0.45$) (39). Background gamma radiation was not assessed.

A large record-based case-control study from Great Britain (GB: England, Wales and Scotland) investigated associations of indoor radon and gamma exposure with various childhood cancers (30). It included 27,447 children diagnosed with cancer during 1980–2006 of which 9,058 were childhood leukaemia. For each case, a control was selected from the same birth register matching for sex and date of birth (within six months). Radiation exposures were estimated for mother's residence at the child's birth. Exposure to gamma radiation was estimated using the County District mean dose rates based on 2,283 indoor measurements made throughout GB. Exposure to radon was estimated using a predictive map based on approximately 400,000 measurements in homes throughout GB. Cumulative doses to the RBM since conception were calculated assuming residential exposures at the same dose rate as the residence of birth. The authors reported a RR for childhood leukaemia of 1.12 (95% CI: 1.03, 1.22) per mSv cumulative equivalent dose to the RBM from terrestrial gamma and 1.03 (95% CI: 0.96, 1.11) for RBM dose from domestic radon.

In Switzerland, two studies, one on radon and another on gamma radiation, were conducted using data from a census-based cohort study (29, 32). Cases of childhood cancer were identified through probabilistic record linkage with the Swiss Childhood Cancer Registry (SCCR). Exposure to residential radon was estimated using a prediction model based on 35,706 indoor measurements and soil and building characteristics (tectonic units, soil texture, floor level and degree of urbanization) as predictors. In internal validation, the radon model had a relatively low R^2 of 0.2. Outdoor dose rates from terrestrial gamma and cosmic radiation were estimated using a map developed by interpolation based on a diverse set of measurements including airborne spectrometry (40). Change of residence between censuses, but not full lifetime residential history, was taken into account to calculate time-varying cumulative exposure. The study on radon exposure included 997 cases of childhood cancer and found no evidence of an association, neither for all cancers combined, nor for leukaemia nor CNS tumours. The study on exposure to gamma radiation included 1,782 cases and found evidence of associations for leukaemia and CNS tumours: for both diagnostic groups a RR of about 1.04 (95% CI: 1.00, 1.08) per mSv cumulative whole-body dose was estimated.

A nationwide case-control study in Finland investigated association between exposure to gamma radiation and childhood leukaemia. It included 1,093 cases diagnosed over the period 1990-2011 (28). Three controls per case, individually matched on year of birth and sex, were selected from the national population register. Exposure was assessed using a map of terrestrial gamma radiation dose rate and a map of Chernobyl fallout. For cases with partially unknown residential history, municipal averages of terrestrial gamma dose rates were used. Exposure assessment accounted for type of building regarding shielding and the radiation from the building materials. Full residential history was available to calculate cumulative dose to the RBM. Overall, there was no evidence of an association for childhood leukaemia (RR 1.01, 95% CI: 0.97, 1.05 for 10 nSv/h increase in average equivalent dose rate to RBM). In subgroup analyses, leukaemia diagnosed at ages 2-6 years was associated with cumulative dose to the RBM (RR 1.27, 95% CI: 1.01, 1.60 per mSv).

In France, a nationwide case-control study investigated the association of childhood acute leukaemia and background radiation (27). It included 2,761 cases diagnosed during 2002-2007 and 30,000 controls sampled from a national dataset of households. Exposure to both radon and gamma radiation was based on cokriging models that combined indoor measurements – 17,404 for gamma (41) and 10,843 for radon (42) – with a map of geogenic radon/uranium potential (R^2=0.32 for radon; R^2=0.65 for gamma). Exposure was assessed based on residence at time of diagnosis. Cumulative doses to the RBM from radon and gamma radiation were calculated assuming constant place of residence since birth. The authors reported an RR for childhood acute leukaemia of 1.00 (95% CI: 0.98, 1.01) per nSv/h of gamma radiation and 0.98 (95% CI: 0.90, 1.07) per 100 Bq/m^3 of radon concentration.

Recently, two ecological studies were conducted in France and Germany. In France, the ecological study assessed cancer risks and exposure across 36,326 municipalities and included 9,056 cases diagnosed between 1990 and 2009. Results were published in parallel with the aforementioned case-control study (27) and used the same exposure models, but exposure was determined at the town centre for radon and at municipality-level means for gamma. Among the 30,000 controls in the case-control study, the municipality-based estimates of exposure used in the ecological study correlated strongly with the estimates of exposure based on residential addresses: r = 0.975 for gamma exposure and r = 0.991 for radon exposure. The results were consistent in both studies and neither showed any

evidence of association between radon or gamma exposure and acute leukaemia or the subgroups ALL or AML. The RR for radon and gamma combined was 1.00 (95% CI 0.99-1.01) per mSv cumulative RBM dose for leukaemia.

The recent nationwide ecological study from Germany (31) investigated childhood cancer risks and gamma ray exposure at the municipality level (11,292 municipalities). The study included childhood cancer cases diagnosed during 1987-2011 with ALL (11,447 cases), AML (1,927 cases), CNS (9,048 cases) and thyroid cancer (230 cases) and a set of childhood cancer diagnoses assumed *a priori* to be unrelated with radiation exposure (11,385 cases) (31). Exposure to terrestrial gamma radiation was assessed for the municipality of residence at diagnosis by interpolation of measured dose rates from the sites of the gamma monitoring network using inverse distance weighting. Data on radon exposure were not available. CNS tumour incidence rates were associated with annual ambient dose rate (RR comparing 1.5 to 0.5 mSv/a of 1.35; 95% CI: 1.17, 1.57). The study did not find evidence of an association with ALL or AML. The ambient dose rate data were extrapolated from 1,800 outdoor measuring sites to the 11,292 inhabited communities. Exposure was assessed only at time of diagnosis.

Methodological challenges

In contrast to earlier studies (14, 25, 26) that were often limited by potential for selection bias and/or limited statistical power (23, 43, 44) , the more recent record-based studies reviewed here do not require active participation of the study population. They thus can achieve larger sample sizes, while essentially avoiding selection bias.

Kheifets et al. evaluated potential bias due to low participation in previous measurement-based studies compared to more recent record-based studies. Overall, associations were stronger for studies based on modelling as compared to ones with measurements. However, only the UK provides sufficient information for appropriate comparison (44). Despite this inherent advantage of studies that are purely record-based, achieving large sample sizes remains a challenge, particularly for countries with small population sizes such as Switzerland, Finland, or Denmark. The greatest challenge of record-based studies, however, is how to accurately assess individual exposure.

Sample size and statistical power

Achieving sufficient statistical power is a key challenge of any epidemiological study assessing cancer risks associated with low-dose radiation. Statistical power depends not only on sample size and the magnitude of the expected effects, but also on the variability of the exposure between subjects.

Three of the reviewed studies reported power calculations (27, 28, 30). For GB, Little et al. computed the number of years of comprehensive cancer registration that would be required to achieve sufficient sample sizes to detect the expected effects of radon and background gamma combined on childhood leukaemia risk (23). Depending on the study design the resulting numbers were: 14 years (6,400 cases) for a cohort study, 17 years (7,800 cases) for a case-control study with 5 controls per case and 19 years (8,700 cases) for an ecological study. The authors assumed the linear low-dose part of the BEIR V model derived from the Japanese data (ERR=32.1 Sv^{-1}) and required 80% power for a 1-sided test at the 5% significance level. Larger samples are required for investigating effects of radon and gamma radiation separately (23).

Despite the large sample size, the statistical power of the recent GB study to detect expected association between gamma ray exposure and childhood leukaemia risk was only about 50% (30); the geographic matching (by birth registration district) of cases and controls combined with the county district averaging resulted in about half of the cases having the same gamma dose rate estimate as their controls. The attempt to mitigate possible spatial confounding by regional matching reduced the exposure contrast between cases and controls and with that also the statistical power of the study. For radon, there were considerably more measurements and the areal units were smaller, so this problem does not apply to the radon analysis, but the RBM dose is smaller and statistical power is much lower for this measure.

The power of the recent French study (27) to detect the expected effects predicted by the multiplicative ERR model published by UNSCEAR (1) for leukaemia was 92.4% for gamma radiation exposure, 44.8% for radon exposure, and 99.4% for total gamma and radon exposure combined. Statistical power was higher for assumed ERRs of 5% and 10% per mSv, which correspond to effect sizes an order of magnitude greater than that found in the GB and Swiss studies. Despite this, no evidence of an association was found, while confidence intervals were incompatible with those of the

study from GB. This discrepancy is unlikely to be due to chance, suggesting that there are biases in either or both studies, or that the effects genuinely differ. The timing of the exposure assessment, which was at birth in the study from GB and at diagnosis in the French study, is one apparent methodological difference that might partially explain the difference. Assuming that early life exposure has a greater effect on cancer risk, exposure assessment at birth should give larger effect estimates (4, 45). However, this explanation is tenable only if residential mobility, i.e. moving home between birth and diagnosis, causes large and systematic differences in exposure between birth and diagnosis, which seems unlikely (see below for a discussion on residential mobility and potential biases).

If the sample size calculations by Little et al. are used as a reference, the smaller studies conducted in Switzerland, Finland, and Denmark were markedly underpowered. However, in countries with greater exposure variability and/or levels, smaller samples are needed to achieve the same statistical power and precision of estimates. In the Swiss study, for instance, gamma-ray dose rate ranged from 55 to 383 nSv/hr (mean 109 nSv/hr) compared to 38-160 nGy/hr (mean 95 nGy/hr) in GB as used in the generic calculations of Little et al. It should be noted that in the GB study of Kendall et al. controls were chosen from the same birth registration district as the case, so the power of this study will be determined by the variability of dose rates within these districts. Bespoke power calculations for the study of Kendall et al. were carried out and reported in that paper. The Finnish study had a statistical power of 80% for detecting a linear dose-response with OR of 1.06 or greater per 10 nSv h^{-1} increase in dose rate. For radon, the differences in exposure variability are larger between countries than for gamma radiation (**Table 3**).

The uncertainty of dose estimates was not accounted for in the power calculations cited above. Its impact could be important (46), but to take it into account would require appropriately specified measurement error models. Further calculations on statistical power that account for the differences in exposure distribution by country and for measurement error are needed.

Separate power calculations are also needed for the investigation of diagnostic subgroups including the cytogenetic subtypes of leukaemia, which may differ in their aetiology. Recurrent cytogenetic

alterations are important prognostic indicators. However, the epidemiological study of such subtypes has only recently begun (47). Of the studies presented in this review, only the Finnish study investigated genetic subtypes and results suggested a larger effect of radiation on leukaemia with high hyperdiploidy than other subgroups.

Exposure assessment and measurement error

One of the reasons why previous studies have focused on residential radon and terrestrial gamma radiation, and not for instance on ingested radionuclides, is that the former natural sources of radiation show distinct and measurable spatial variation. Such spatial variation can be exploited for exposure assessment in record-based studies based on residential information. Some countries, particularly those with considerable topographic variation, have included cosmic radiation, which can be modelled as a direct function of elevation (1). While concentrations of naturally occurring radionuclides in the soil, a major source of gamma radiation, are relatively constant over time, temporal variation due to migration and decay of radionuclides from artificial sources, such as the Chernobyl nuclear accident, may also be relevant.

Exposure to terrestrial gamma and cosmic radiation

In record-based studies, levels of external background gamma radiation in the homes of study participants are predicted based on measurements made at other locations throughout the area of study. There is considerable heterogeneity between the studies in the types of measurements and methods used (**Table 3**). Both indoor and outdoor measurements have been used for this purpose. Methods for assessing exposure in the study population include taking averages over administrative units, simple methods of interpolation, and global modelling approaches including kriging methods. The computational resolution of the maps ranged between 1x1 km^2 (France) and 8x8 km^2 (Finland).

Clearly, these models do not capture all sources of exposure variation. Indoor exposure depends strongly on radioactivity in building characteristics including materials, shielding effects and the time children spend indoors and outdoors. Even though measured indoor dose rates correlate with outdoor dose rates, as shown in Finland as well as in GB (28, 48), exposure estimates derived from indoor measurements are anticipated to be more reliable as children spend most of their time indoors.

However, if relevant building characteristics are not accounted for in the exposure model and differ considerably between children's homes or between measurement sites and children's homes, this advantage could be lost. Although several studies based exposure assessment on indoor measurements, only the Finnish study included information on building type (blocks of flats compared to single-family houses and terraced houses) in the exposure model.

Another neglected source of variation are exposures outside the home, such as at schools. The true exposure of a child will be a weighted average of exposure at multiple locations within some perimeter from their home, suggesting that perfect spatial resolution of exposure models may not be needed for accurate prediction of individual exposure.

Lastly, rainfall can modulate exposure by washing out the decay products of radon, leading to short-term spikes in measurable radiation levels at ground-level, while snow cover can have a shielding effect. The latter may have led to an overestimation of the radiation levels in alpine regions of Switzerland, as variations due to snow coverage were not considered.

There is also heterogeneity in the sources of external background gamma radiation considered for exposure assessment. Not all studies included the cosmic component, which is preferable if dose rates from cosmic rays vary considerably within the area of study. The studies from Finland and Switzerland separately modelled dose contributions originating from the Chernobyl fallout. In Switzerland, the dose rates from ^{137}Cs were separately assessed and added to the other components of terrestrial radiation without considering temporal variation due to decay and migration of caesium.

Residential radon

Compared to gamma dose-rates, radon concentration is more difficult to model, because of large spatial variations in the radon potential of underlying soils and the strong dependency on housing characteristics and individual behaviour such as ventilation and heating habits. Reliable information on these predictors is seldom available. Therefore, there is arguably greater potential for misclassification when modelling radon compared to gamma. Again, there is considerable heterogeneity between the studies in the methods used to predict radon exposure (**Table 4**).

In the GB study, alternative methods for estimating radon concentrations were tested. The first grouped measurements by geological boundaries and grid squares; the second used simple averages over County Districts. Broadly, similar results were obtained with either model (49).

Radon is the dominant source of effective dose from natural sources of radiation in the general population. However, most of this dose is delivered to the lung and the contribution from radon to red bone marrow doses, which are relevant for the development of leukaemia, is minor compared to ingested radionuclides, terrestrial and cosmic radiation. For children in GB, Kendall et al. (50) estimated a mean annual RBM dose at ages 0-14 of 1.4 mSv with radon being responsible for around 6% of the total dose, while terrestrial gamma rays with directly ionising cosmic rays and ingested radionuclides are responsible of 50% and 39% of the total dose, respectively. Harley and Robbins (51) have suggested that doses from radon decay products to circulating lymphocytes in the tracheobronchial epithelium could be relevant for childhood ALL, although Little et al. (10) concluded that it remains reasonable to concentrate attention upon the dose to the RBM when assessing the radiation-related risk of childhood leukaemia.

The effects on childhood leukaemia risks of radon exposure are presumably more difficult to detect than those of gamma ray exposure, given a greater potential for exposure misclassification and a lower contribution to RBM doses.

Performance of exposure models

The performance of exposure models is generally assessed by leaving a set of measurements (test sample) out and predict its value based on the remaining measurements (training sample). In such internal validation, the coefficients of determination (proportion of variance explained, R^2) of models used to assess residential radon exposure ranged from 0.20 to 0.40 (**Table 4**). The Danish study, the only study to use an independent dataset for validation (external validation), reported an R^2 of 0.45 (39).

The performance of models used to estimate exposure to gamma radiation has been rarely assessed. In GB, gamma exposure was assessed using a simple county district mean, but in recent years several alternative prediction models based on gamma measurements in GB (48, 52, 53) have been devised.

The best performance was found for a linear model based on weighted sums of gamma dose rates among neighbouring measurement points and other simple models (53), which might be used in future studies. In France, the model used to estimate gamma exposure was based on Warnery et al. (41) and validated against an independent set of 8,839 dwelling indoor measurements (54). A relatively good correlation (r = 0.59) between estimates and measurements was observed, but there was a significant difference in mean dose rates (76 vs 55 nSv/h), possibly reflecting a difference between the dental surgeries and veterinary clinics, where the measurements used for model development had been made, and dwellings. In a sensitivity analysis, using an exposure model based on these 8,839 measurements within dwellings (unpublished results) rather than on the 17,404 ones used in the published analyses (27, 54), the findings of the study were unchanged.

To date, there has been no validation of the exposure models used in the reviewed studies based on personal dosimetry in children. Such a study could help better understand the errors of the exposure models (55).

Neglected sources of exposure

Doses from medical uses of radiation and ingested radionuclides have been largely neglected in studies of cancer risks from background radiation, because data acquisition is exceedingly difficult, particularly without active participation of the study population. The Finnish study evaluated various hypothetical bias scenarios due to doses from CT scan examinations, but results were not materially affected (28). To the extent that omitted exposures correlate with the exposures that were assessed and included in regression models, estimated dose response relationships may be biased. Given a likely correlation between exposure to residential radon and exposure to terrestrial gamma radiation (30) , (organ-specific) doses from these sources should be combined, but dose conversion models for radon exposure are not well established as yet. Detailed information regarding possible correlations between these exposures and doses from ingested radionuclides or from medical radiation is lacking. A correlation of exposure to gamma radiation or domestic radon with doses from ingested radionuclides is plausible as the latter may also depend on local or regional concentrations of naturally occurring radionuclides. Such correlations would be more likely if consumed food products are grown locally

and drinking water is sourced from local aquifers. To some extent homeostatic control of ^{40}K concentrations will reduce the variation in doses from internal emitters in the body, but such mechanisms do not apply to other radionuclides (56).

Residential mobility and timing of exposure assessment

Another important question that arises in studies of childhood cancer and natural sources of radiation is whether complete residential histories are required for accurate assessment of cancer risks. Radiation doses from gamma and radon exposure are received continuously over the whole lifetime at dose rates that are approximately constant at a given residential location (although radon remediation measures could substantially reduce radon exposure). The extent to which cancer risks at a given attained age depend on doses received at earlier ages remains unclear. Existing models suggest that these relationships differ considerably between cancer types (57). In the absence of an agreed alternative weighting scheme, cumulative doses are calculated by (unweighted) integration of dose-rates from conception (or birth) to attained age. Ideally, this calculation should be based on full residential history. However, such data are only available in a few, mainly Nordic countries. In Finland, Nikkilä et al. examined the effects of incomplete residential histories on studies of background radiation (58). About 48% of cases and controls had lived only at one address and those who had relocated generally only moved short distances (median 4km, mean 40km) resulting in small differences in exposure levels between successive addresses. Similarly, Demoury et al. found only about 34% of children moved to another municipality between birth and diagnosis, and that there was a high correlation between exposures at birth and at diagnosis or at inclusion in control group: the Pearson correlation coefficient was 0.86 for radon and 0.89 for gamma radiation (27). Of the childhood cancer cases in the study from GB, 44% had not moved residence between birth and diagnosis, and about two-thirds were living at diagnosis within 2 km of their birth address (43). Thus, in the absence of data on full address histories, the estimation from a single address, despite introducing measurement error, should still capture a large proportion of exposure variability between individuals.

Potential confounding

Potential confounders comprise non-radiation risk factors that are associated with the primary disease endpoint and with determinants of radiation exposure from natural sources, such as residential location, dwelling characteristics and inhabitants' living habits. Some factors for which a link with childhood cancer is supported by the literature and that might be associated with radiation exposure (29, 59) include traffic-related air pollution (60), pesticides (61), exposure to infections (62-66) and socioeconomic status (SES) (59, 67-69).

Such association may also exist for other factors discussed in the literature of childhood cancer, for instance: genetic syndromes (47) and birth weight (70). Although all studies had considered some of these factors, it is difficult for a single study to include all (**Table 1**). The studies from France, Switzerland and Denmark included a broad range of covariates that showed some correlation with gamma or radon exposure. However, these adjustments had little effect on estimates of interest.

Overall assessment of potential errors and bias

Despite the methodological challenges, record-based studies have potential to detect and quantify childhood cancer risks associated with natural sources of radiation. First, by design, these studies are virtually free of selection bias (assuming complete cancer registries and random sample of representative controls) and the larger studies are adequately powered. Though exposure assessment is difficult, we would argue that the consequences of measurement errors may not be as severe as one might expect. The methods of estimating individual exposure to natural sources of radiation in record-based studies involve interpolation, smoothing of measurements, and thus have a tendency for regression to the (local) mean. Arguably, therefore, the dominant component of non-systematic exposure measurement error in the discussed studies is of Berkson type, which results in reduced precision and statistical power, rather than of classical type, which would lead to bias towards the null. Furthermore, exposure models that, to a certain extent, smooth out small-scale variation may even improve precision of individual exposure assessment, because children's true exposure is a time-weighted average of exposures at the various locations (indoors and outdoors) where they spend most of their time. Lastly, the risk of confounding may be minimal, because for most of the suspected risk

factors neither the correlations between background gamma or radon nor the effects of the latter on the risks of childhood cancer are likely to be strong. Furthermore, in none of the studies did adjustment for potential confounders, such as SES, appreciably alter effect estimates.

Despite these grounds for optimism, the excess cancer risks associated with natural background radiation are expected to be small and, consequently, even small biases from unmeasured confounding or measurement error could obscure the true effects. In consequence, the potential for bias should not be neglected. Indeed, the discrepancies between the results of the reviewed studies might suggest that systematic errors are at work in some way.

Systematic errors in exposure estimates might occur if the measurements on which these are based are not representative of exposure levels at the locations where the study subjects spend much of their time. However, such errors are unlikely to cause bias in effect estimates unless they differ systematically between cases and controls. Other potential sources of systematic error could include regional differences in cancer registration coverage that correlate with natural sources of radiation levels, neglected exposures, large-scale confounding, ecologic bias or biases associated with aggregating (or over-smoothing) the exposure (71), and sampling variation, among others.

Conclusions and future perspectives

Recent studies on exposure to natural sources of radiation and childhood cancer have shown conflicting results, which remain to be resolved. As we have outlined, these studies face some common methodological challenges that should be addressed in future research. We propose some steps forward in **Box 1**. Thanks to the early establishment of national cancer registries in some countries, the challenge of achieving sufficient statistical power can now be met. Nevertheless, still larger studies or the pooling of studies will be needed to investigate disease subgroups.

Currently, the greater challenge is to accurately assess children's exposure for such large study populations. For this, the study groups should learn from each other and join in concerted efforts to improve exposure estimation and look for new ways to validate these models with personal dosimetry. Quantitative analysis of potential biases associated with exposure misclassification and unmeasured confounding could shed light on existing inconsistencies and help study designs in future studies. By

addressing these challenges, we are reasonably confident that studies on exposure to natural sources of radiation and cancer risks in children can provide an evidence base for a better understanding of the effects of low dose ionizing radiation.

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Box 1: Recommendations for future research on cancer risks associated with natural sources of radiation

- Increase sample size by including more recent cases and by pooling studies in order to assess effects on diagnostic subgroups and cytogenetic subtypes
- Pool studies that have information on full residential history to assess the effects of timing of exposure
- Optimise and harmonise methodologies for exposure modelling across studies
- Refine exposure models for gamma radiation by accounting for shielding effects and radioactivity of building materials
- Conduct focused exposure studies that will allow validation of exposure models used:
    - Surveys that assess individual exposure using personal dosimeters and collect information on time spent indoors and outdoors, housing characteristics, and perimeter of daily movements
    - New measurements at locations where children spend much of their time (schools, playgrounds etc.)
- Refine and harmonise dosimetric calculations of cumulative organ doses throughout childhood
- Include quantitative analysis and simulation of possible biases under realistic assumptions of measurement error and residual confounding

Tables

Table 1. Characteristics of recent nationwide record-based epidemiological studies on background radiation and childhood cancer

	Denmark	**Great Britain**	**Switzerland**	**Switzerland**	**Finland**	**France**	**France**	**Germany**
Study	Raaschou-Nielsen et al. 2008	Kendall et al. 2013	Hauri et al. 2013	Spycher et al. 2015	Nikkilä et al. 2016	Demoury et al. 2017	Demoury et al. 2017	Spix et al. 2017
Study design	case-control	case-control	census-based cohort	census-based cohort	case-control	ecological (municipal level)	case-control	Ecological (community level)
Period	1968 - 1994	1980 - 2006	all children living in Switzerland 2000	1990-2008	1990 - 2011	1990 – 2009	2002-2007	1987–2011
Total number of cases-controls	2,400-6,697	27,447-36,793	997	1,782	1,093-3,279	9,056	2,763-30,000	22,652
Leukaemia cases	1,153	9,058	283	530	1,093	9,056	2,763	13,374
Brain and CNS tumours	922	6,585	258	423				9,048
Malignant lymphoma	325	2,319		328				

Source of cancer cases	Danish Cancer Registry	National Registry of Childhood Tumours	Swiss Childhood Cancer Registry	Swiss Childhood Cancer Registry	Finnish Cancer Register	National Registry of Childhood Cancers	National Registry of Childhood Cancers	German Childhood Cancer Registry
Selection of controls/population								
Method	2 controls for each case of leukaemia, 3 for each case of CNS tumour, and 5 for each malignant lymphoma, matched on sex and date of birth, randomly drawn from registry	1 or 2 controls per case matched on sex, date of birth and place of birth registration	Resident population < 16 years of age during national census in 2000	Resident population < 16 years of age during national censuses in 1990 and 2000	3 controls per case matched on year of birth and gender	Census data from 1990 - 2009	30,000 contemporaneous control addresses (5,000 per year) randomly sampled	Population data from 1987 - 2011 for the West and 1991 - 2011 for the East
Source	Danish Central Population Registry	Birth registry	Swiss National Cohort	Swiss National Cohort	Population Register Centre	Censuses	Income and council tax databases of households	Federal Statistics Bureau

Covariates at individual level	birth order, mother's age, traffic density, electromagnetic fields from nearby high voltage facilities	birth register, social class of the father (from occupation), Socio-economic status at census ward level (Carstairs index)	sex, age, residential mobility, birth order, socioeconomic status of the parents, distance to road, NO2, regions, electric power lines, benzene concentrations, distance to broadcast transmitters, distance to the nearest orchard and vineyard, golf course, and gamma radiation	education of household reference person, crowding, birth weight, birth order, traffic - related air pollution, electromagnetic fields from radio and TV transmitters, high voltage power lines	Down syndrome, large for gestational age, maternal smoking during pregnancy	age, sex, exclusion of Paris	age, sex, exclusion of Paris, exclusion of vicinity of nuclear power plants, proximity to high-voltage power lines, proximity to high traffic road	age

Covariates at group level				degree of urbanization of municipality, socio-economic status of municipality		socio-economic status of the municipality (Fdep index)	socio-economic status of the municipality (Fdep index)	Socio-economic index on community level, regions, excluding big cities
Exposure assessment								
Included exposures	Indoor radon	Indoor radon Indoor gamma Cosmic radiation	Indoor radon	Terrestrial gamma Cosmic radiation Cs-137 deposition	Indoor and outdoor gamma Chernobyl fallout	Indoor radon Terrestrial gamma Cosmic radiation	Indoor radon Terrestrial gamma Cosmic radiation	Outdoor gamma
Timing of exposure	residential address history	at birth	at census	at census	residential address history	at diagnosis	at diagnosis	at diagnosis
Gamma dose range (mean)	-----	38.1 - 159.7 nGy/hr (94.7 nGy/hr)	-----	55 - 383 nSv/hr (109 nSv/hr)	Mean: 67.2 nSv/h for cases and 66.4 nSv/h for controls	65.9 - 260.8 nSv/hr (102.6 nSv)	65.9 - 260.8 nSv/hr (102.6 nSv)	56.9 – 172.0 nSv/hr (93.3 nSv/h)

Radon exposure range (mean)	4 - 254 Bq/m3 (48 Bq/m3)	1.2 - 692 Bq/m3 (21.3 Bq/m3)	0.7 - 490.1 Bq/m3 (86 Bq/m3)	-----	-----	12.5 - 819.2 Bq/m3 (67.2 Bq/m3)	12.5 - 819.2 Bq/m3 (67.2 Bq/m3)	-----
Statistical analysis								
Risk measure	Rate ratios for cumulative exposure	Relative risk for cumulative exposure	Hazard ratios for survival data	Hazard ratios for survival data	Odds ratio for cumulative exposure and average exposure	Standardized incidence ratio for cumulative and at place of diagnosis exposure	Odds ratio for cumulative and at place of diagnosis exposure	Incidence rate ratios
Latency period	-----	9 months	-----	-----	24 months	0 and 24 months	0 and 24 months	-----

Table 2. Relative risks in recent nationwide record-based epidemiological studies on background radiation and childhood leukaemia

Source of exposure	Country	Cases	Time-place of exposure	Relative risks (95% confidence interval)	
				Leukaemia	Central Nervous System tumours
Radon concentration (Bq/m3)					
	DK	1,153	Full residential history	1.34 (0.97, 1.85)[a/]	0.92 (0.69, 1.22)[a/]
	CH	283	Census	0.90 (0.68,1.19)[b/]	1.19 (0.91, 1.57) [b/]
Radon radiation dose (mSv)					
	GB	9,058	Birth	1.03 (0.96, 1.11)	
	FR	9,056	Diagnosis	1.00 (0.97, 1.02)	-
Gamma radiation dose (mSv)					
	GB	9,058	Birth	1.12 (1.03, 1.22)	
	FI	1,093	Full residential history	0.97 (0.89, 1.06)	-

	FR	9,056	Diagnosis	1.00 (0.99, 1.01)	-
	CH	530	Census	1.04 (1.00, 1.08)[c/]	1.04 (1.00, 1.08)[c/]
	DE	11,447	Diagnosis	1.04 (0.91, 1.20)[d/]	1.35 (1.17, 1.57)[d/]
Radon and background gamma dose combined (mSv)					
	GB	9,058	Birth	1.07 (1.01, 1.13)	-
	FR	9,056	Diagnosis	1.00 (0.99, 1.01)	-

Note: data are relative risk (95% confidence intervals) per mSv cumulative equivalent dose to the RBM (if not otherwise indicated). Abbreviations: FI Finland, GB Great Britain, FR France, CH Switzerland, DK Denmark and DE Germany.

[a] Per 10^3 Bq/m^3-years

[b] Per 100 Bq/m^3

[c] Per mSv cumulative effective dose (whole body)

[d] RR comparing 1.5 vs 0.5 mSv/a for acute lymphoid leukaemia

Table 3: Characteristics of models use to assess exposure on gamma radiation in recent record-based epidemiological studies on background radiation and childhood cancer

	Great Britain	**Switzerland**	**Finland**	**France**	**Germany**
Study	Kendall et al. 2013	Spycher et al. 2015	Nikkilä et al. 2016	Demoury et al. 2017	Spix et al. 2017
Exposure assessment	Indoor dose rates from cosmic and terrestrial sources	Outdoor dose rates from cosmic and terrestrial sources	Indoor and outdoor dose rates from terrestrial sources	Indoor dose rates from cosmic and terrestrial sources	Outdoor annual ambient dose rate from terrestrial and cosmic sources
Sources	2,283 domestic measurements in Great Britain	Airborne spectrometry, 166 in-situ spectrometry measurements, 837 in situ dose rate measurements, and 612 laboratory measurements of rock and soil	346 domestic measurements, a mobile survey with Geiger-counters and spectrometers, Municipal averages of dose rates, Map of Cs-137 activity after Chernobyl nuclear accident,	- Terrestrial gamma radiation: 14,124 measurements (8,895 indoor, 5,229 outdoor) and 14,234 TLD measurements in surveillance data. - Telluric gamma radiation: Map of geogenic uranium potential and 97,595 TLD measurements in dentist	1,800 stations in Germany

			Building material information as an indoor/outdoor factor	surgeries and veterinary clinics - Ecological study: average municipality exposure	
Type of model	County districts mean	Interpolation using inverse distance weighting	Bivariate interpolation	Cokriging	Interpolation using inverse distance weighting
Geographic resolution	County District level	2×2 km^2 grid map	8 x 8 km grid map	1 × 1 km^2 grid map	Community level

Table 4. Characteristics of radon exposure assessment in recent record-based epidemiological studies on background radiation and childhood cancer

	Denmark	**Great Britain**	**Switzerland**	**France**
Study	Raaschou-Nielsen et al. 2008	Kendall et al. 2013	Hauri et al. 2013	Demoury et al. 2017
Exposure assessment	Domestic radon concentration	Domestic radon concentration	Domestic radon concentration	Domestic radon concentration
Sources	3,116 indoor measurements	~400,000 indoor measurements,	35,706 indoor measurements	10,843 measurement of indoor radon
Predictors	Geographical region, soil type and house characteristics	Bedrock and superficial geological characteristics	Tectonic units, building information, soil texture, urbanization and floor level	concentration and a map of geogenic radon potential
Performance	$R^2 = 0.45$ (tested against independent measurements)	$R^2 = 0.34$ - 0.40	$R^2 = 0.20$	$R^2 = 0.32$
Method	Linear regression model	Log-normal modelling based on measurements grouped by grid square and geological boundaries	Log-linear regression model	Cokriging model
Geographic resolution		1×1 km^2 grid map		1×1 km^2 grid map