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Review

A Brief Review of Case-control Studies of Natural Background Radiation and Childhood Cancer in Great Britain

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Studies of natural radiation and childhood cancer must be very large if they are to have sufficient power to detect the very small radiation effects expected. Conventional interview-based case control studies with a sufficiently large number of study subjects would be exceptionally expensive and would also be liable to bias which might lead to confounding that would dominate the results of the study. Record based studies, in which cases and controls are drawn from existing registers, have the potential to be large enough and to avoid the risk of bias. However, they will not have interview-based information on factors such as Socioeconomic Status, nor will they have direct measurements of radiation levels in the homes of study subjects. A large record-based case control study from Great Britain is reviewed here in the context of such case-control studies generally. This study has detected a statistically significant association between indoor gamma ray exposures and the incidence of childhood leukaemia. The risk factor was compatible with that extrapolated from higher dose studies, in particular those of the Atomic Bomb Survivors.

Key words: cancer, childhood, radiation, radon, gamma rays

Calculations based on recent radiation risk models suggest that natural background radiation causes around 15-20% of all childhood leukaemia cases in Great Britain (GB)[1]. A number of epidemiological studies have investigated whether this excess could be detected. These are briefly reviewed here with emphasis on a recent record-based case-control study. The paper is based on a presentation at the Educational Symposium on Radiation and Health (ESRAH), May 2015.

Amongst previous studies, perhaps the most significant was the UK Childhood Cancer Study (UKCCS). This was a large interview-based case-control study designed to investigate five broad hypotheses relevant to the aetiology of childhood cancer, including ionising radiation. The UKCCS included data for 3838 cases and 7629 controls collected in the early- to mid-1990s[2]. Here we restrict our attention to the two papers published on indoor radon[3]

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and on indoor gamma-rays[4].

The UKCCS gamma-ray study[4] involved 2165 eligible cases of childhood cancer and analyzed in terms of the gamma-ray dose-rate in the dwelling occupied at the time of diagnosis. There was no indication of increased risk with increasing gamma-ray dose-rate and the investigators concluded that "It is unlikely that the expected small association would be detectable". Statistical power calculations confirm this suggestion – assuming linear extrapolation of risk from the Japanese atomic bomb survivor data, epidemiological studies require at least 8,000 cases of childhood leukaemia (which comprise about one third of all childhood cancers) in order to have sufficient power (>80%) to detect the effect of natural background radiation at the levels found in GB[5]. It is noteworthy that only about 56% of the original total number of cases could be included in the UKCCS gamma-ray analysis.

The UKCCS radon study[3] included a similar number of eligible cases (2226). However, in contrast to the gamma-ray study, strongly decreasing cancer risks with increasing radon concentrations were found. The investigators did not regard this as causal and suggested "This could have arisen because of differences not adequately allowed for in the deprivation scores": the loss of study subjects had almost certainly introduced a bias because it was differential across SES (SocioEconomic Status) groupings. While 87% of cases were enrolled only 64% of controls could be included, and the enrolment of first choice controls varied with SES deprivation index from 82% for category 1 (least deprived) to 45% for category 7 (most deprived). In GB, both mean indoor radon concentrations and leukaemia rates vary with SES, supporting the explanation suggested by the UKCCS investigators for the negative association.

The conclusion must be that a very large and well conducted interview-based case-control study failed to detect the effect of natural background radiation on childhood cancer risk because it was under-powered and suffered from participation bias. However, an alternative approach may avoid these problems.

Record-based case-control studies make use of pre-existing databases. They do not attempt to interview or make individual contact with the study subjects. This carries with it two very substantial advantages: the studies can be very big and they are free of response bias. There are concomitant disadvantages: there are no measurements of exposures directly related to study subjects and no data from interviews to provide information on, for example, residential histories. We now give a concise summary of a record-based case-control study of naturally occurring radiation and the incidence of childhood cancer in GB. The first phase of this study has been published[6, 7] and fuller details can be found in these publications.

Cases were those born and diagnosed in GB during 1980-2006 and were drawn from the National Registry of Childhood Tumours (NRCT)[8]. Matched controls (one control per case up to 2000, two controls per case thereafter) were also available. The total number of cases was 27,447, of which 9058 were leukaemias. The number of controls was 36,793.

Basic information from birth records, such as date of and maternal residence at birth, are available for study subjects. Generally (for 94% of study subjects) the Address-Point location of the birth address is available, but in some cases we have only the somewhat less precise Code-Point location. These georeferencing schemes are described by Martin and Higgs[9]. Swanson *et al.*[10] reported that Address-Point grid references are typically accurate to a few metres and Code-Point grid references to a few tens of metres. Address at diagnosis is known for cases, but the equivalent information is not available for controls. Full residential histories (i.e., details of all dwellings occupied between birth and diagnosis) are not known. Controls for the NRCT were drawn from the same birth register as the corresponding cases and this results in a degree of geographical matching; about half the cases are in the same county district (CD, an intermediately sized administrative area) as their control(s).

Two sources of information on SES are available for study subjects:

- Carstairs index of deprivation[11] calculated for census wards (small areas, which contain on average about 5000 people)
- Father's Social Class based on occupation as given on the child's birth certificate. This is self-reported and incomplete (it is available for about 90% of study subjects).

Two types of radiation exposure were considered in the study, indoor gamma-rays and indoor radon, but measures of radiation exposure were not available from the NRCT so other sources of information had to be used.

Estimates of indoor gamma-ray exposures were based on a National Survey of indoor exposure to naturally occurring radiation sources[12]. In the National Survey, two TLD dosemeters were exposed for six months in a living room and the main bedroom of participants and a weighted sum of the two results was taken as the value for the house. The dosemeters were sensitive not only to terrestrial gamma-rays but also to the directly ionising component of cosmic-rays and it what follows the two are considered together; that is, analyses were carried out in terms of the sum of dose (or dose-rate) from the two components. A total of 2283 gamma-ray measurements from the National Survey were available to the present investigators. From these data we estimated means for

Table 1. Summary of the results of the British record-based childhood cancer case-control study (Kendall *et al.*, 2013). Trend analysis by diagnostic grouping

	Cases	Odds Ratio	95% CI	*P*
Results for radon				
Lymphoid Leukaemia	7,267	1.24	0.94-1.64	0.13
Total Leukaemia	9,058	1.12	0.88-1.43	0.35
All Other cancers	18,389	1.06	0.91-1.24	0.43
All Childhood Cancer	27,447	1.08	0.95-1.23	0.25
Results for gamma-rays				
Lymphoid Leukaemia	7,267	1.10	1.02-1.19	0.01
Total Leukaemia	9,058	1.09	1.02-1.17	0.01
All Other cancers	18,389	1.02	0.98-1.06	0.38
All Childhood Cancer	27,447	1.03	1.00-1.07	0.04

Lymphoid leukaemia is ICCC3 code 11; all leukaemia is codes 11-15. All other cancers are codes 21-122. The odds ratios are for each 10^3 Bq/m^3-years increase in cumulative radon exposure and per each mGy increase in cumulative gamma-ray dose, respectively

the 459 English CDs and comparable administrative units in Scotland and Wales (in brief "CDs"). The average number of measurements per CD was five.

Two measures of indoor radon exposure were available. Firstly, means for CDs based on data of National Survey (these are the analogues of gamma-ray estimates). Secondly, more precise estimates were available from a predictive map based on domestic measurements grouped by geological boundaries[13] ("Miles/Appleton" estimates).

The analysis used conditional logistic regression. The main analysis considered the cumulative dose from birth to diagnosis, roughly equivalent to the period between conception and diagnosis, less a latent period of nine months; however, a variety of latent periods were considered. Both radiation doses and SES were included in the models – Carstairs Quintile was used in the main analysis, but Carstairs score and father's social class were also used. The main analysis included both gamma-ray and radon doses separately. The Appleton/Miles radon estimates were used for the main analysis, but CD averages were also considered.

Table 1 gives the main results of the trend analysis for radon dose and for gamma-ray dose.

For radon all odds ratios are above 1.0, but none are close to being statistically significant. For gamma-rays, for the grouping of childhood cancers other than leukaemia the odds ratio is above one, but not close to significance. However, the leukaemia odds ratio is elevated (1.09) and significant (P=0.01).

Broadly similar results are obtained for variants on the main analysis (see section 4 of report[7]):

1. Different measures of SES: Carstairs quintile, Carstairs score, father's occupation, no SES adjustment.
2. Different measures of radon exposure: Appleton/Miles estimates, A/M estimates based only on Address-Point, CD averages, no radon exposure estimates included.
3. Different latent periods: 0, 9, 12, 24 months

The gamma-ray results of Table 1 are equivalent to a 12% (95% CI: 3%, 22%; two-sided p=0.01) proportional increase in the risk of childhood leukaemia per millisievert of cumulative red bone marrow dose from gamma radiation[6]. This is broadly compatible with risk estimates indicated by UNSCEAR and by BEIR VI[6]. For radon the analogous association was not significant, a proportional increase in risk of 3% (95% CI: -4%, 11%; p=0.35) per mSv red bone marrow dose. Associations for other childhood cancers were not significant for either gamma-ray or radon exposure.

The most striking finding was the statistically significant positive trend in the risk of childhood leukaemia with increasing cumulative dose of naturally occurring gamma radiation, of a magnitude comparable to that predicted by previous calculations based on recent standard risk and dose models. Excess risks were largely insensitive to adjustment for different measures of SES, to different estimates of radon exposure or to different assumed minimum latent periods. The excess risk was compatible with the estimates derived from risk models developed by UNSCEAR and BEIR VI.

Is a cause-and-effect interpretation of the association found in this study for childhood leukaemia and natural background gamma radiation plausible? The study is of reasonable statistical power (in round terms, ~50% [6]) and is free of those problems of bias that can arise in interview-based case-control studies.

Might the significant finding be a result of confounding? It is impossible to prove the absence of unexpected and undetected confounding in any epidemiological study: all that can be done is to investigate specific possibilities. The authors have been unable to identify any confounders that might correlate with exposure to natural background gamma radiation; adjustment for two measures of SES did

not affect the association. Given the pattern of results – the association between childhood leukaemia and cumulative gamma-ray dose is around the level predicted by recent risk models, and the absence of any other association is as expected – we regard this association between childhood leukaemia and naturally occurring gamma-rays as likely to be causal.

Nevertheless, the study has weaknesses. Foremost amongst these is the use of CD averages as a measure of individual gamma-ray exposures. This results in a loss of information (in that study subjects within the same CD will generally experience different gamma-ray dose-rates) and also reduces the power of the study because approaching half the cases were born in the same CD as their matched control(s).

A second phase of the GB record-based case-control study of natural background radiation and childhood cancer is in preparation. This will consider a longer calendar period (1962-2010, instead of 1980-2006) and will thus include more study subjects: provisionally ~ 54,500 cases instead of 27,447, and ~ 70,000 controls instead of 36,793. It will also make use of individual gamma-ray estimates that are specific to the particular birth addresses of study subjects, rather than relying on areal averages. This is possible because of an enlarged set of gamma-ray dose-rate measurements (10,199 instead of 2,283) thanks to data from the UKCCS, to whom we are very grateful. A prime task of the second analysis will be to explore the effect of replacing CD average gamma estimates with individual values.

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Disclosure

The authors declare that they have no conflict of interest.

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