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Effects of incomplete residential histories on studies of environmental exposure with application to childhood leukaemia and background radiation

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ABSTRACT

When evaluating environmental exposures, residential exposures are often most relevant. In most countries, it is impossible to establish full residential histories. In recent publications, childhood leukaemia and background radiation have been studied with and without full residential histories. This paper investigates the consequences of lacking such full data.

Data from a nationwide Finnish Case-Control study of Childhood Leukaemia and gamma rays were analysed. This included 1093 children diagnosed with leukaemia in Finland in 1990–2011. Each case was matched by gender and year of birth to three controls. Full residential histories were available. The dose estimates were based on outdoor background radiation measurements. The indoor dose rates were obtained with a dwelling type specific conversion coefficient and the individual time-weighted mean red bone marrow dose rates were calculated using age-specific indoor occupancy and the age and gender of the child. Radiation from Chernobyl fallout was included and a 2-year latency period assumed.

The median separation between successive dwellings was 3.4 km and median difference in red bone marrow dose 2.9 nSv/h. The Pearson correlation between the indoor red bone marrow dose rates of successive dwellings was 0.62 (95% CI 0.60, 0.64). The odds ratio for a 10 nSv/h increase in dose rate with full residential histories was 1.01 (95% CI 0.97, 1.05). Similar odds ratios were calculated with dose rates based on only the first dwelling (1.02, 95% CI 0.99, 1.05) and only the last dwelling (1.00, 95% CI 0.98, 1.03) and for subjects who had lived only in a single dwelling (1.05, 95% CI 0.98, 1.10).

Knowledge of full residential histories would always be the option of choice. However, due to the strong correlation between exposure estimates in successive dwellings and the uncertainty about the most relevant exposure period, estimation of overall exposure level from a single address is also informative. Error in dose estimation is likely to cause some degree of classical measurement error resulting in bias towards the null.

1. Introduction

Environmental exposure is often determined by location. Because children typically spend most of their time at home (UNSCEAR, 2000), residential exposures, also known as domestic exposures, are often most relevant. Examples include residential exposure to background radiation for residential radon and terrestrial gamma rays, electromagnetic fields and air pollution (Kroll et al., 2010; Raaschou-Nielsen et al., 2001; UK Childhood Cancer Study Investigators, 1999).

Children are more susceptible to the carcinogenic effects of ionising radiation than adults, and many studies of natural radiation and cancer have focused on children (Demoury et al., 2017; Kendall et al., 2013; Nikkilä et al., 2016; Raaschou-Nielsen et al., 2008; Spix et al., 2017; Spycher et al., 2015). Such studies must include thousands of cases in order to achieve sufficient statistical power to detect the small effects expected from ambient exposures, as extrapolated from high dose levels (Little et al., 2010). However collecting information on such large samples through interview or direct measurement is expensive and prone to selection bias. In most

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countries, it is impossible to establish full residential histories, i.e. a list of dwellings occupied with dates of moving in and out, without individual contact with study subjects. Only few countries, including the Nordic countries, have nationwide registries that provide such data. For this reason, many such studies have limited exposure assessment to a single dwelling, for example that occupied at diagnosis (UK Childhood Cancer Study Investigators, 2002a, 2002b; Demoury, 2017) or that at birth (Kendall et al., 2013).

Because direct measures of natural radiation are impracticable, exposure is usually estimated from models. The indoor dose rates of terrestrial gamma radiation depend on outdoor dose rates, the shielding effect of the material of the house, and the radiation emitted by the building materials. Reasonable predictions of indoor gamma-ray dose rates can be made based on location and factors such as geology and socioeconomic status of the area (Chernyavskiy et al., 2016; Kendall et al., 2016; Warnery et al., 2015). Nevertheless, considerable inter-house variation remains. In the British studies, the residual Mean Square Error (MSE) was 378 $(nGy/h)^2$ on a mean estimate of 96 nGy/h; in France MSE = 407 $(nSv/h)^2$ with a mean of 76 nSv/h. Such significant uncertainties can be avoided only by direct measurement in the house in question or, potentially, by modelling using more detailed information, in particular on the radioactive content of all significant building materials used in each dwelling (European Commission, 1997). Similar considerations apply, perhaps with even more force, to indoor radon concentrations – neighbouring houses can differ greatly in a random, time varying and unpredictable way, but models can make reasonable predictions for areal averages (Miles and Appleton, 2005).

In studies of the effects of protracted exposures to ionising radiation (or other agents) it is necessary to consider how susceptibility varies over the exposure period. This is particularly important in the context of background radiation, as doses are accumulated throughout life and children are known to be more susceptible (UNSCEAR, 2008a). The extent to which susceptibility varies throughout childhood is unknown though there is evidence that susceptibility is greatest at younger ages (National Research Council NRC, 2006; UNSCEAR, 2008a, 2013). A reasonable approach is to use total cumulative dose or time-integrated dose rates from birth or conception to diagnosis as exposure measure. However, it is possible that, for example, exposures around the time of birth or during pregnancy are disproportionately important (ICRP: International Commission on Radiological Protection, 2003; National Research Council NRC, 2006; UNSCEAR, 2013).

A recent publication from the Finnish Register-based Case-Control study of Childhood Leukaemia (FRECCLE) (Nikkilä et al., 2016), on the effect of natural gamma rays on risk of childhood leukaemia made use of a nationwide population registry in order to obtain complete residential histories for the study subjects. The present paper analyses these data in more detail to obtain insights for the interpretation of similar epidemiological studies, which lack the richness of the data available in Finland.

It is the aim of this paper

i) to investigate patterns of residential mobility, or migration, in families with young children,
ii) to investigate the extent to which doses in successive dwellings vary and
iii) to examine the implications of residential mobility for epidemiological studies of natural gamma rays and childhood cancers in general and leukaemia in particular.

2. Materials and methods

FRECCLE includes 1093 children diagnosed with leukaemia in Finland in 1990–2011, identified from the Finnish Cancer Registry. Each case was matched by gender and year of birth to three controls at the Population Register Centre. For the matched cases and controls, the Population Register Centre provided complete residential histories from birth to the reference date (date of diagnosis for cases; for controls, date when an exposure period of similar length is reached). These residential histories included moving dates and municipalities of residence, as well as coordinates, building type and identification codes for each residence.

The ambient dose estimates are based on an 8 × 8 km gridded map of outdoor natural background radiation from the Finnish Radiation and Nuclear Safety Authority. This map is based on the measurements from a mobile survey carried out between 1978 and 1980 in Finland (Arvela et al., 1995). The indoor dose rates were obtained with a conversion coefficient specific to the dwelling type and the individual time-weighted red bone marrow dose rate averages were calculated using age-specific indoor occupancy coefficients and the age and gender of the child (Arvela et al., 1995; Kendall et al., 2009; Mäkeläinen et al., 2005). Radiation from Chernobyl fallout was also modelled, though its contribution to the total dose estimates was small (~3%) (Nikkilä et al., 2016). The median dose rate to red bone marrow (Chernobyl and natural background radiation) was 67.2 nSv/h for cases and 66.4 nSv/h for controls.

Based on previous studies, Nikkilä et al. (2016) assumed a 2-year minimum latency period in their main analysis resulting in zero exposure for subjects younger than 2 years at the reference date (in utero exposure was ignored) (UNSCEAR, 2008b). The odds ratio (OR) of childhood leukaemia was calculated for every 10 nSv/h increase in time-weighted average indoor gamma-ray dose-rate over the period from birth to the reference date. For the present work other measures of exposure were investigated as described in the Results section.

Statistical analyses were done using R (3.4.0) and conditional logistic regression was used for matched case-control data. The ethical committee of Pirkanmaa Hospital district reviewed the study protocol (tracking number R14074). According to Finnish regulations, no informed consent was required for a register-based study.

3. Results

Table 1 shows the number of dwellings occupied by cases and by controls in the Finnish study (Nikkilä et al., 2016). These numbers take into account the two-year latency period, so that subjects aged less than 2 years at their reference date (156 cases and 468 controls) were excluded, leaving 937 cases and 2811 controls for analysis. About 48% of both cases and controls had lived at only one address between birth and the reference date. Five percent of both cases and controls had lived in five or more dwellings during the exposure period. The mean number of addresses occupied between birth and the reference date was approximately 1.9 for both cases and controls. In total, there were 63 (0.8%) residencies abroad. The percentage of cases who moved during the two-year latency period preceding the reference date was 26.0% and 26.2% for controls.

Table 2 shows the separation (km) and mean difference in dose rate for different pairs of addresses for cases and controls separately. The first of these is equivalent to the separation of two randomly chosen dwellings in our Finnish dataset; the median is similar to the mean for cases and controls (cases: 233 km vs. 267 km, controls: 230 km vs. 264 km). Successive homes of the same family are, on average, much closer together, with a median separation of only 3.4 km (cases: 3.6 km, controls: 3.3 km). The mean distance between successive dwellings of the same family is an order of magnitude larger than the median, because of the influence of relatively uncommon long-distance moves (i.e. the distribution is highly skewed). The separation of the first and last dwellings occupied by a family is a little larger than the separation of successive homes, but broadly similar. The dose rates varied as might be expected, with successive dwellings of the same family having the lowest changes in dose rate.

The Pearson correlation coefficients with their 95% confidence intervals for four selected pairs of dose-rate variables ("scenarios") are presented in the Table 3. For all scenarios, the indoor and outdoor dose rates for all study subjects were analysed separately. The correlation coefficient between indoor gamma dose rates for two successive dwellings occupied by study subjects was 0.62 (95% CI 0.60, 0.64). The correlation between the dose rates at the first and the last dwelling occupied by the study subjects was 0.67 (95% CI 0.65, 0.70). The correlation between the indoor dose rate averaged over all the subject's dwellings and the dose rate inside the first dwelling was 0.78 (95% CI 0.76, 0.80). The respective values of these correlation coefficients for outdoor dose rates were higher. The Pearson