

INDOOR RADON AND CHILDHOOD LEUKAEMIA

Ole Raaschou-Nielsen*

Institute of Cancer Epidemiology, Danish Cancer Society, Strandboulevarden 49,
2100 Copenhagen Ø, Denmark

This paper summarises the epidemiological literature on domestic exposure to radon and risk for childhood leukaemia. The results of 12 ecological studies show a consistent pattern of higher incidence and mortality rates for childhood leukaemia in areas with higher average indoor radon concentrations. Although the results of such studies are useful to generate hypotheses, they must be interpreted with caution, as the data were aggregated and analysed for geographical areas and not for individuals. The seven available case–control studies of childhood leukaemia with measurement of radon concentrations in the residences of cases and controls gave mixed results, however, with some indication of a weak (relative risk < 2) association with acute lymphoblastic leukaemia. The epidemiological evidence to date suggests that an association between indoor exposure to radon and childhood leukaemia might exist, but is weak. More case–control studies are needed, with sufficient statistical power to detect weak associations and based on designs and methods that minimise misclassification of exposure and provide a high participation rate and low potential selection bias.

INTRODUCTION

Few risk factors have been established for childhood leukaemia. One is high doses of ionising radiation, but it is unclear whether a low-dose of radiation, such as alpha radiation from indoor ^{222}Ra and progeny (denoted collectively as radon in the following text), is also a risk factor. Exposure to radon is known to cause lung cancer^(1–3), but the dose of radiation to the red bone marrow after exposure to radon in air is much lower than that to the lung and bronchial epithelium. Dosimetric calculations have indicated that ~6% of childhood leukaemias in the UK might be due to domestic radon⁽⁴⁾. A review by Laurier *et al.*⁽⁵⁾ concluded that the overall epidemiological results available at that time did not suggest an association between radon exposure and leukaemia.

A number of ecological studies have shown associations between mean radon levels and childhood leukaemia incidence and mortality rates^(6–17), which have fuelled the hypothesis that indoor radon causes childhood leukaemia. The ecological studies on radon and childhood leukaemia were reviewed by Laurier *et al.*⁽⁵⁾ and another three studies showed ecological associations subsequently. The results of ecological studies must, however, be interpreted with caution, and individual-level case–control studies are needed to test the hypothesis. Domestic concentrations of radon were measured in six case–control studies of childhood leukaemia, which, however, gave inconsistent results. Most recently, a newly developed and validated prediction model was used in a large nationwide Danish study to calculate indoor radon levels in the homes of children with

cancer and control children⁽¹⁸⁾. The study showed a significant association between cumulated radon exposure and risk for acute lymphoblastic leukaemia (ALL) in children.

ECOLOGICAL STUDIES

A number of ecological studies have addressed the associations between mean levels of radon and age-standardised incidence^(6–10,12–17) or mortality rates⁽¹¹⁾ for leukaemia across geographical areas. Exposure in an area was usually measured as the mean radon concentration in indoor air^(6–10,12–14,16,17), but the concentrations in drinking water⁽¹¹⁾ and at ground level⁽¹⁵⁾ have also been used. Most studies addressed all childhood leukaemias combined, but ALL and acute myeloid leukaemia (AML) have also been studied separately. Associations were expressed as correlation coefficients, linear regression coefficients or rate ratios. Most of the studies were conducted in the UK^(6,9,10,12–14), and others in France^(16,17), Sweden⁽¹⁵⁾ and the USA⁽¹¹⁾. International comparisons were made in two of the studies^(7,8).

Since ecological studies on radon and childhood leukaemia were reviewed by Laurier *et al.*⁽⁵⁾, three further studies have been published. Kohli *et al.*⁽¹⁵⁾ divided the Swedish province of Östergötland into three areas according to the concentration of radon at ground level, and 68 506 children born in the province between 1979 and 1992 were followed-up for incident malignancies in the local cancer registry between 1979 and 1995, providing a total of 90 cases of which 22 were ALL. The standardised incidence rates for all cancers combined did not differ significantly among the three areas, but an association was observed with ALL. When the incidence rate for

*Corresponding author: ole@cancer.dk

ALL in the area with the lowest radon concentration was used for comparison, the rate ratio was 4.6 (95% CI: 1.3–28.3) for the area with medium concentration and 5.7 (95% CI: 1.1–42.3) for the high-radon area. Evrard *et al.*⁽¹⁶⁾ studied the mean indoor radon concentrations and acute leukaemia incidence in 348 geographical units (zones d'emploi) in France between 1990 and 1998, with 4015 cases registered by the French National Registry of Childhood Leukaemia and Lymphoma. The mean indoor radon concentrations varied from 15 to 387 Bq m⁻³ in the 348 areas. The results showed a 24% (95% CI: 8–44%) increase in the standardised incidence ratio (SIR) for AML and a 3% (95% CI: –5–11%) increase in the SIR for ALL per 100 Bq m⁻³ increase in mean radon concentration. These results were confirmed in a subsequent study on another geographical scale, with a longer period and within different strata of cosmic gamma radiation⁽¹⁷⁾.

Altogether, the results of the 12 ecological studies are remarkably consistent in that 11 showed a positive association between radon level and childhood leukaemia, 8 with statistically significant associations (Table 1). One study showed a non-significant inverse association. All four studies of ALL showed positive associations, three of them statistically significant. The two studies of AML showed statistically significant associations. Table 1 summarises the 12 ecological studies.

CASE–CONTROL STUDIES

In 1987, Stjernfeldt *et al.*⁽¹⁹⁾ published the first case–control study on indoor radon and childhood leukaemia, with seven acute leukaemia cases living in the Östergötland region of Sweden. The mean radon concentration measured in the last houses occupied by the leukaemia cases was 156 Bq m⁻³ and that for the matched controls was 333 Bq m⁻³.

In a study in the USA involving 942 eligible cases and 1292 eligible controls, radon measurements in homes inhabited for more than 70% of the childhood period were available for 505 cases (54%) and 443 (34%) controls. The unmatched analysis provided an odds ratio for ALL of 1.44 (95% CI: 0.9–2.3) for >148 Bq m⁻³ compared with <37 Bq m⁻³⁽²⁰⁾. The matched analysis gave a rate ratio of 1.02 (95% CI: 0.5–2.0) on the basis of 281 cases (30% of those eligible) and 281 matched controls (22% of those eligible).

Kaletsch *et al.*⁽²¹⁾ measured radon in the homes occupied for at least 1 y of 82 children with acute leukaemia (primarily ALL) and 209 controls in Lower Saxony, Germany, corresponding to 40% of eligible cases and 34% of eligible controls. The results showed an odds ratio of 1.30 (95% CI: 0.32–

5.33) for an exposure contrast of >70 versus <70 Bq m⁻³.

Steinbuch *et al.*⁽²²⁾ studied the association between radon measured in the homes of 173 children when diagnosed with AML and 254 controls in Canada and the USA. The children corresponded to 80% of cases and 86% of controls eligible for the measurement study and 27% of cases and 33% of controls available for the interview study. The study showed an overall odds ratio of 1.1 (95% CI: 0.6–2.0) for a domestic radon concentration of >100 Bq m⁻³ when compared with <37 Bq m⁻³, and an association of borderline significance after exclusion of children younger than 2 y. The authors concluded that the latter result might have been due to chance.

Maged *et al.*⁽²³⁾ measured radon in homes occupied in Cairo, Egypt, since birth of 50 children with ALL and 110 control children. The study showed significant associations between radon and risk for ALL, with odds ratios of 5–7 for the higher exposure categories. These risk estimates are far higher than those in the other case–control studies.

In a large study in the UK, radon was measured in the homes at the time of diagnosis of 2226 children with cancer (50% of eligible cases) and 3773 control children (31% of those eligible)⁽²⁴⁾. The study showed a lower risk in association with higher radon levels for all types of childhood cancer, including ALL with an odds ratio of 0.77 (95% CI: 0.61–0.99) and other leukaemias with an odds ratio of 0.71 (95% CI: 0.43–1.19) for exposures >30 Bq m⁻³ compared with those <8 Bq m⁻³. The authors of the study suggested that the consistent inverse association might have been related to socioeconomic and household differences between the cases and controls that were not observed because of the high rate of non-participation.

In a recent Danish study, the hypothesis tested was that exposure to domestic radon increases the risk for leukaemia and other childhood cancers⁽¹⁸⁾. Incident cases of leukaemia ($n = 1153$), central nervous system tumour ($n = 922$) and malignant lymphoma ($n = 325$) diagnosed in children between 1968 and 1994 were identified in the Danish Cancer Registry, and 6697 control children were selected from the Danish Central Population Registry. A newly developed and validated prediction model⁽²⁵⁾ was used to calculate the radon concentrations in the children's residences. The cumulated exposure of each child was calculated as the product of 'exposure level and time', cumulated for all addresses occupied during childhood. Cumulated radon exposure was associated with the risk for ALL, with rate ratios of 1.21 (95% CI: 0.98–1.49) for $0.26–0.89 \times 10^3$ Bq m⁻³ y and 1.63 (95% CI: 1.05–2.53) for exposure to $>0.89 \times 10^3$ Bq m⁻³ y when compared with $<0.26 \times 10^3$ Bq m⁻³ y. For a 5-y-old child, this

Table 1. Ecological studies of radon and childhood leukaemia.

Reference	Country	Period	Type of leukaemia (number of cases)	Incidence/ mortality	Estimation of exposure to radon	Number of units	Direction of association	Significance
Lucie ⁽⁶⁾	UK	1984–86	ALL (187)	Incidence	Indoor measurements	22 counties	+	$p < 0.01$
Henshaw <i>et al.</i> ⁽⁷⁾	International	Not given	L	Incidence	Indoor measurements	13 countries	+	$p < 0.02$
Butland <i>et al.</i> ⁽⁸⁾	International	Not given	L	Incidence	Indoor measurements	7 countries	+	NS
Alexander <i>et al.</i> ⁽⁹⁾	UK	1984–88	ALL	Incidence	Indoor measurements	22 counties	+	$p < 0.005$
Muirhead <i>et al.</i> ⁽¹⁰⁾	UK	1969–83	L	Incidence	Indoor measurements	22 counties (459 districts)	+	NS
Collman <i>et al.</i> ⁽¹¹⁾	USA	1950–79	L (1194)	Mortality	Water supply concentration	Three groups (100 counties)	+	$p < 0.05$
Foreman <i>et al.</i> ⁽¹²⁾	UK	1976–85	L (245)	Incidence	Indoor measurements	Two groups (four counties)	–	NS
Richardson <i>et al.</i> ⁽¹³⁾	UK	1969–83	L (6691)	Incidence	Indoor measurements	402 districts	+	NS
Thorne <i>et al.</i> ⁽¹⁴⁾	UK	1976–95	AML	Incidence	Indoor measurements	Two groups	+	$p < 0.05$
Kohli <i>et al.</i> ⁽¹⁵⁾	Sweden	1979–95	ALL (22)	Incidence	Ground radon levels	13 municipalities (one county)	+	$p < 0.05$
Evrard <i>et al.</i> ⁽¹⁶⁾	France	1990–98	ALL (3239) AML (697)	Incidence	Indoor measurements	443 zones	ALL: + AML: +	ALL: $p = 0.49$ AML: $p = 0.004$
Evrard <i>et al.</i> ⁽¹⁷⁾	France	1990–2001	ALL (4346) AML (912)	Incidence	Indoor measurements	95 departements	ALL: + AML: +	ALL: $p = 0.88$ AML: $p = 0.02$

L, all leukaemias; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia.

difference in cumulated exposure would correspond to concentrations >178 versus <52 Bq m⁻³. A linear dose-response analysis showed a 56% increase in the rate of ALL per 10³ Bq m⁻³ y increase in exposure. The association with ALL persisted in sensitivity analyses and after adjustment for potential confounders. If a causal association is assumed, an estimated 9% of ALL cases in Denmark would be attributable to domestic exposure to radon. No statistically significant association was found for other types of leukaemia or other types of childhood cancer included.

Table 2 summarises the results of the seven published case-control studies on domestic exposure to radon and childhood leukaemia. Figure 1 illustrates the results of five studies that gave results for ALL and two studies that reported on acute non-lymphoblastic leukaemia (ANLL). One study showed a much higher relative risk⁽²³⁾ than the others, and another showed an apparently protective effect of radon⁽²⁴⁾, whereas the other three studies indicated a weak association between indoor exposure to radon and the risk for childhood ALL^(18,20,21). The two studies that addressed radon exposure and the risk for ANLL in children indicated no association^(18,22).

DISCUSSION

Eleven of 12 ecological studies have shown positive associations between average regional radon level and incidence and mortality rates of childhood leukaemia; eight of the studies showed significant associations. Seven case-control studies of childhood leukaemia and radon have been conducted, with mixed results. The studies are discussed below, with a focus on the choice of design and methods in order to guide future studies.

The ecological studies consistently showed associations between area radon levels and rates of childhood leukaemia, for both ALL and AML. Half of the studies, however, are from the same country (the UK), and several were not independent from each other because the populations overlapped. Further, it is well recognised that ecological studies should be interpreted with caution, because the data are aggregated and analysed for geographical units and not for individuals⁽⁵⁾. Domestic radon concentrations can vary substantially within a small area and even between neighbours because of differences in house construction and the airing habits of the inhabitants. Moreover, adjustment for potential confounders is rare in ecological designs. Thus, although the ecological studies form a solid basis for the hypothesis that domestic exposure to radon causes childhood leukaemia, case-control studies with assessment of individual exposure are essential in order to test the hypothesis.

Few case-control studies on this topic have been published. Five studies were published on the risk for ALL, and the results of two of them can be considered outliers in each direction, as one gave extremely high relative risk estimates given the limited dose of radiation from indoor exposure to radon and the other showed apparently protective effects of indoor exposure to radon against childhood ALL (and all other types of childhood cancer). The remaining three studies all indicated a weak association between indoor exposure to radon and childhood ALL, although the association was statistically significant in only one of the studies. The relative risk estimates for the group with the highest exposure compared with a reference group with low exposure were all less than or equal to 1.6. Only two studies addressed indoor exposure to radon and childhood ANLL, both indicating no association. Thus, the case-control studies indicate that, if a causal association between indoor radon and childhood leukaemia exists, the effect of radon is probably relatively weak. Thus, future studies should be large enough to have sufficient statistical power to detect weak associations.

In six of the seven case-control studies, exposure was assessed from measurements in the homes of children, whereas a validated prediction model was used in one study⁽²⁵⁾. These methods each have their advantages and disadvantages. Measurements reflect the concentration in the home during the period of measurement and also, in contrast to the prediction model, reflect the actual airing habits of the inhabitants; however, this method for assessing exposure requires the cooperation of the families and access to the homes (and perhaps to former homes) of cases and controls, which limited the participation rate in these studies. Low participation rates imply a risk for selection bias, in particular if the participation rates of cases and controls differ, which can affect the risk estimates in a case-control study in either direction. The low participation rates, which differed for cases and controls, were suggested to be the explanation for the apparently protective effect of indoor radon on the risk for childhood leukaemia and other types of childhood cancer found in one study⁽²⁴⁾. Future case-control studies would benefit from new ways of ensuring high participation rates. High participation can be ensured by calculating radon concentrations in homes, as the 'participation' rate depends on whether input data for the model can be obtained for cases and controls. Misclassification of exposure must be expected when using prediction models, however, and the degree of misclassification should be evaluated and reported to allow proper interpretation of the results, particularly if they show no significant association between radon exposure and childhood leukaemia.

Table 2. Case-control studies of residential exposure to radon and childhood leukaemia.

Reference	Country	Period	Type of leukaemia	Cases/controls	Age (years)	Matching criteria	Participation rates of cases/controls	Estimation of radon exposure	Exposure difference evaluated	Risk estimate (95% CI)
Stjernfeldt <i>et al.</i> ⁽¹⁹⁾	Sweden	1980–84	Five ALL Two AML	7/7	2–11	Age and sex	54% / —	Measurements (2 h) in homes		Cases: 156 Bq m ⁻³ Controls: 333 Bq m ⁻³ RR: 1.02 (0.5–2.0) (matched) OR: 1.44 (0.9–2.3) (unmatched)
Lubin <i>et al.</i> ⁽²⁰⁾	USA	1989–93	ALL	281/281 (matched) 505/443 (unmatched)	0–14	Age, race and place of residence	30/22% (matched analysis) 54/34% (unmatched analysis)	Measurements (1 y) in homes	>148 versus <37 Bq m ⁻³	OR: 1.30 (0.32–5.33) OR: 1.1 (0.6–2.0)
Kaletsch <i>et al.</i> ⁽²¹⁾	Germany	1988–93	AL	82/209	0–14	Age and sex	40/34%	Measurements (1 y) in homes	>70 versus <70 Bq m ⁻³	OR: 1.30 (0.32–5.33)
Steinbuch <i>et al.</i> ⁽²²⁾	USA and Canada	1989–93	AML	173/254	0–17	Age, race and geography	27/33% of those eligible in interview study. 80/86% of those eligible in measurement study	Measurements (1 y) in homes	>100 versus <37 Bq m ⁻³	OR: 1.1 (0.6–2.0)
Maged <i>et al.</i> ⁽²³⁾	Egypt	1996–98	ALL	50/110	2–14	Age and sex	21%/—	Measurements (3 months) in homes	>90 versus <40 Bq m ⁻³	OR: 5.4 (1.3–21.1)
UK Childhood Cancer Study Investigators ⁽²⁴⁾	UK	1992–96	ALL OL ^a	805/1306 146/232	0–14	Age, sex and Family Health Service Authority/Health Board	50/31%	Measurements (6 months) in home	>30 versus <8 Bq m ⁻³	OR (ALL): 0.77 (0.61–0.99) OR (OL): 0.71 (0.43–1.19)
Raaschou-Nielsen <i>et al.</i> ⁽¹⁸⁾	Denmark	1968–94	ALL ANLL OL ^b	860/1720 150/300 143/286	0–14	Age and sex	99/98% 99/98% 94/92%	Calculated radon in homes	>0.89 versus <0.26 × 10 ³ Bq m ⁻³ y ^c	RR (ALL): 1.63 (1.05–2.53) RR (ANLL): 0.60 (0.25–1.41) RR (OL): 1.36 (0.48–3.83)

ALL, acute lymphoblastic leukaemia; ANLL, acute non-lymphoblastic leukaemia; AML, acute myeloid leukaemia; AL, acute leukaemias.

^aOL, leukaemias other than ALL.

^bOL, leukaemias other than ALL or ANLL.

^cFor a 5-y-old child, this difference in cumulated exposure would correspond to >178 versus <52 Bq m⁻³.

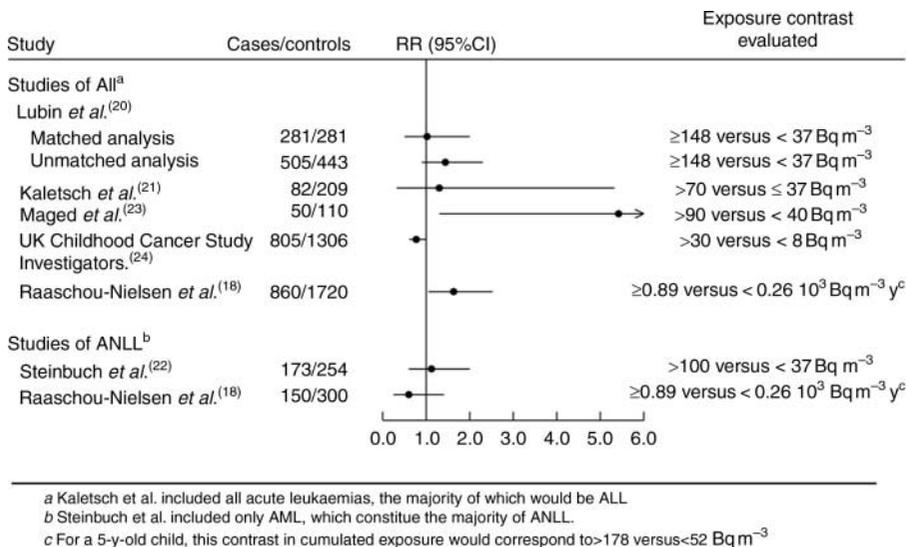


Figure 1. Case-control studies of residential radon and childhood leukaemia.

Another important methodological aspect is the choice of the homes to be included in the exposure assessment, as many children will have lived in more than one home up to the time of diagnosis. A safe choice is to include all the addresses at which cases and controls lived throughout childhood, which facilitates calculation of cumulated exposure over the entire period from time of birth until time of diagnosis, and a similar period for controls. This strategy for selecting addresses also facilitates analyses of exposure time windows of potential importance for the risk for developing leukaemia, and it minimises the risk for bias due to potential differences in the movement patterns of cases and controls.

In summary, the epidemiological evidence suggests that a relatively weak association between exposure to radon and childhood leukaemia might exist. More case-control studies are needed to reach a conclusion. They should be large and based on designs and methods that minimise exposure misclassification and the risk for selection bias due to non-participation.

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