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LEADING ARTICLE

A record-based case–control study of natural background radiation and the incidence of childhood leukaemia and other cancers in Great Britain during 1980–2006

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We conducted a large record-based case–control study testing associations between childhood cancer and natural background radiation. Cases (27 447) born and diagnosed in Great Britain during 1980–2006 and matched cancer-free controls (36 793) were from the National Registry of Childhood Tumours. Radiation exposures were estimated for mother's residence at the child's birth from national databases, using the County District mean for gamma rays, and a predictive map based on domestic measurements grouped by geological boundaries for radon. There was 12% excess relative risk (ERR) (95% CI 3, 22; two-sided $P = 0.01$) of childhood leukaemia per millisievert of cumulative red bone marrow dose from gamma radiation; the analogous association for radon was not significant, ERR 3% (95% CI -4, 11; $P = 0.35$). Associations for other childhood cancers were not significant for either exposure. Excess risk was insensitive to adjustment for measures of socio-economic status. The statistically significant leukaemia risk reported in this reasonably powered study (power $\sim$50%) is consistent with high-dose rate predictions. Substantial bias is unlikely, and we cannot identify mechanisms by which confounding might plausibly account for the association, which we regard as likely to be causal. The study supports the extrapolation of high-dose rate risk models to protracted exposures at natural background exposure levels.

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Keywords: cancer; childhood; radiation; radon; gamma rays

INTRODUCTION

There is abundant evidence that exposure to ionising radiation can cause cancer, particularly from data on the survivors of the Japanese atomic bombings and other groups receiving moderate or high doses at high-dose rates.[1] Ionising radiation is one of the few established exogenous risk factors for childhood leukaemia,[2] but again this evidence derives mainly from groups exposed to moderate or high doses and high-dose rates.[1]

A long-standing question is whether cancer risks detected in moderate/high dose and high-dose rate studies can be extrapolated to low doses or low-dose rates (which may be taken to be, respectively, <100 and <5 mGy/h of sparsely ionising radiation[3,4]). For example, some claim thresholds in the dose response for cancer, or even beneficial effects at low doses,[5] although the basis of this claim has been challenged.[6] Calculations, based on risk models derived from the atomic bomb survivors[7,8] suggest that about 15% of childhood leukaemia incidence in Great Britain is attributable to ubiquitous exposure to natural background radiation, although the uncertainties associated with this estimate are substantial. Many epidemiological studies have examined the putative association between childhood leukaemia and exposure to radiation from natural sources.[9–14] Although positive associations have been reported from some studies,[9–14] their interpretation has been problematical due to study deficiencies, for example participation bias, liability to 'ecological bias', or their being severely underpowered.[15]

A recent example of an investigation of the possible effects of natural background radiation upon the risk of childhood cancer is the UK Childhood Cancer Study (UKCCS), a large interview-based case–control study of childhood cancer throughout Great Britain during the early 1990s.[16] It was set up to examine five possible causitive factors, one of which was exposure to ionising radiation *in utero* or after birth, and the findings of analyses of exposure to gamma rays[13] and to radon[12] have been published. No association between gamma-ray exposure and the risk of any of the main types of childhood cancer was found, but as our calculations indicate[15] and as the UKCCS authors surmised, the gamma-ray branch of the study was underpowered. A negative association between the level of radon exposure and risk of childhood cancer (with similar patterns for each diagnostic grouping) was found, but our calculations indicate that the radon branch of the study had even less statistical power than the gamma-ray part. Moreover, the UKCCS suffered from incomplete and differential participation and the authors regarded this finding as artefactual, concluding that socio-economic differences between cases and controls, and between first choice controls and those actually interviewed, probably accounted for the observations.

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We report here a record-based case–control study investigating the effects of natural background radiation exposure on childhood leukaemia and other cancers, which is far larger than previous case–control studies. Our study design is similar to that of a record-based case–control study recently conducted in Denmark,[14] but it considers gamma rays as well as radon and is an order of magnitude larger, and therefore of much greater power.

MATERIALS AND METHODS

A fuller description of Materials and Methods is given in Supplementary Appendix 1.

The study population was children born and diagnosed with cancer or nonmalignant brain tumour in Great Britain between 1980 and 2006, recorded on the National Registry of Childhood Tumours,[17] an essentially complete population-based registry of cancers diagnosed in Great Britain before the fifteenth birthday. Birth registration details were available for almost all births in Britain. In all, 1 or 2 controls matched on sex and date of birth (to within 6 months) had already been selected from the same birth register as the case; 27 447 cases and 36 793 controls resulted.

Addresses of mothers at the time of birth of their child were assigned grid references using the ADDRESS-POINT system or, if this was not possible (about 4% of records), the less precise Code-Point.[18,19]

Ionising radiation exposure of cases and controls was estimated from the place of residence of the mother at the child's birth. Data on indoor absorbed dose rates from gamma rays with the directly ionising component of cosmic rays came from the National Survey of natural background radiation based on measurements made in 2283 houses in Great Britain;[20] for brevity we denote these as 'gamma-ray dose'. For this study we used mean gamma-ray dose rates in 459 English County Districts and comparable administrative areas in Wales and Scotland.[21]

Two sources of radon concentration estimates in the homes of study participants were used:

1. Mean exposures in County Districts, from the National Survey;[20] the radon analogues of the gamma-ray estimates.
2. A predictive radon map developed by the Health Protection Agency and British Geological Survey (HPA/BGS), which was based on the results of about 400 000 measurements of radon concentrations in homes grouped by grid squares and boundaries between different geological units.[22–24]

Our main analyses use gamma--ray-absorbed dose rate and radon concentration integrated from birth to diagnosis, approximating exposure from conception to 9 months before diagnosis. We also investigate other minimum latent periods of 0, 12 and 24 months, defined as the periods from birth to diagnosis: plus 9 months (approximating conception to diagnosis), minus 3 months (approximating conception to 12 months before diagnosis) and minus 15 months (approximating conception to 24 months before diagnosis).

The measured dosimetric quantities are proportional to tissue doses from the two components separately. To compare the risk estimates from this study with published estimates, it is necessary to calculate doses to the target tissue in question, and if the risks from gamma rays and radon are to be examined together doses from both sources must be calculated on the same basis. This could be done only for leukaemia, for which the relevant quantity is the red bone marrow (RBM) equivalent dose.

Socio-economic status (SES) is known to influence rates of childhood cancer, particularly leukaemia.[25] The principal measure of SES considered in the analysis was the Carstairs deprivation index, based upon the census ward in which the mother was living during the child's birth;[26] the main analysis included quintiles of the Carstairs index. Carstairs scores were available for all cases and controls in the study. An alternative measure of SES was the social class of the father, derived from his occupation as stated on the child's birth record. The occupational description was coded and social class category derived using classifications used by the Office of Population Censuses and Surveys, now the Office for National Statistics.[27,28] Paternal occupational social class derived in this way was available for about 90% of cases and controls and was based on self-reported data, which were sometimes ambiguous, although any inaccuracies should not be differential between cases and controls; analyses were restricted to the 85% of matched sets where both case and control(s) were assigned a value.

The analysis used conditional logistic regression (within matched case-control sets)[29] implemented in STATA.[30] In the main analysis a log-linear logistic model was fitted via maximum likelihood,[29] in which $RR_i = \exp[\alpha_1 D_i + \alpha_2 S_i]$ (D_i = cumulative lagged dose, S_i = Carstairs score). Confidence intervals (CI) were Wald-based, calculated using the Fisher information.[31] The *P*-values presented were calculated from likelihood ratio tests, and were two-sided.

RESULTS

Table 1 gives a breakdown of the number of cases and controls by age at diagnosis. Tables S1 and S2 give the breakdown of cases and controls by, respectively, calendar year of birth and diagnosis, and age at diagnosis. When comparisons are made between cases and their matched controls the mean absolute difference (that is, regardless of whether positive or negative) between the dates of birth is 13.5 days, with 95% being within 5 weeks. However, controls were born both before and after their matching case and the mean difference is less than 1 day.

Further details, including information on migration of cases (that is, from the birth address by the time of diagnosis) are presented in Tables S3–S5; equivalent migration information for controls is not available. For all childhood cancers combined, address at diagnosis was the same as address at birth for about 50% of cases and a further 20% had moved <2 km. Of those diagnosed in the first years of life, 96% still resided in the County District (CD) in which they were born, whereas for those diagnosed at age 14 years this figure dropped to 75%; over the age range 0–14 years, 83% had not moved CD before diagnosis. Clearly, the proportion of cases that had moved by the time of diagnosis increases with age at diagnosis, and thus varies somewhat with cancer type (Tables S3, S4) being rather higher for lymphomas (mean age at diagnosis 8.9 years). The mean separation between maternal residence at birth of cases and matched controls is about 11 km.

Table S6 gives a breakdown of the study population by Carstairs quintile and by father's social class as deduced from his occupation as given on the birth certificate. The proportion of cases and that of controls in the various categories were similar.

Estimates of indoor gamma-ray dose rate and radon concentration are available for all cases and controls. The approximate matching of cases and controls on place of birth results in a proportion of case–control sets having the same estimated radiation exposure. This arises more frequently for the gamma-ray dose rate, which is determined by the CD of maternal residence at the child's birth. The number of cases with a gamma-ray dose rate different from their control(s) was 14 308 (52% of all cases), whereas over 95% of cases and controls were assigned different radon concentrations. If gamma-ray dose rates or radon concentrations are the same for cases and controls then cumulative doses will differ only because of differences in the at-risk periods, although typically this results in smaller differences in cumulative doses than from different dose rates or concentrations.

Gamma-ray dose rates were distributed approximately normally with a mean for controls of 94.7 (SD 15.6; range 38.1–159.7) nGy/h, whereas radon concentrations were approximately log-normally distributed with a geometric mean of 16.4 and a geometric SD of 2.0 (arithmetic mean 21.3 and SD 22.6; range 1.2–692) Bq/m^3 for controls. The observation of log-normal distributions of radon concentrations is a common one.[32,33] However, the dose accumulated between birth and diagnosis is of greater aetiological relevance than dose rates or activity concentrations, and this depends on the age at diagnosis for the disease in question. Distributions of gamma-ray doses by attained age for cases and controls are given in Table S7 for the disease groupings

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Table 1. Distribution of numbers of cases and controls by grouped age at diagnosis and diagnostic grouping

Disease grouping	*ICCC3 codes*	*Age group (years)*					*Mean age (years)*
		<1	*1–4*	*5–9*	*10–14*	*0–14*	
Cases							
Lymphoid leukaemia	11	337	4182	1904	844	7267	5.1
Acute myeloid leukaemia	12	237	521	288	270	1316	5.2
Other leukaemias	13–15	115	190	91	79	475	4.7
Total leukaemia	11–15	689	4893	2283	1193	9058	5.1
Hodgkin lymphoma	21	0	82	275	582	939	10.6
Non-Hodgkin lymphoma except Burkitt lymphoma	22	14	273	371	325	983	7.8
All lymphomas	21–25	23	468	803	1025	2319	8.9
Brain and CNS tumours	31–36	584	2351	2231	1419	6585	6.3
Other malignant tumours	41–122	2015	4101	1638	1731	9485	4.8
All cancer except leukaemia	21–122	2622	6920	4672	4175	18 389	5.8
Total childhood cancer	11–122	3311	11 813	6955	5368	27 447	5.6
Males: total childhood cancer	11–122	1760	6447	3953	2945	15 105	5.6
Females: total childhood cancer	11–122	1551	5366	3002	2423	12 342	5.5
Controls							
Lymphoid leukaemia	11	428	5339	2561	1243	9571	5.2
Acute myeloid leukaemia	12	306	649	393	389	1737	5.5
Other leukaemias	13–15	148	226	117	113	604	4.9
Total leukaemia	11–15	882	6214	3071	1745	11 912	5.3
Hodgkin lymphoma	21	0	113	385	890	1388	10.7
Non-Hodgkin lymphoma except Burkitt lymphoma	22	18	333	476	475	1302	8.1
All lymphomas	21–25	29	603	1096	1546	3274	9.2
Brain and CNS tumours	31–36	743	3097	3033	2124	8997	6.5
Other malignant tumours	41–122	2602	5186	2210	2612	12 610	5.1
All cancer except leukaemia	21–122	3374	8886	6339	6282	24 881	6.1
Total childhood cancer	11–122	4256	15 100	9410	8027	36 793	5.8

Abbreviation: CNS, central nervous system.

all leukaemias and in Table S8 for all other cancers. As expected, there is a strong tendency for higher doses to have been accrued by those diagnosed at older ages. Differences between case and control distributions are not obvious by inspection of these data and a comparative analysis as described in Supplementary Appendix 1 is required; the resulting variation in relative risk (RR) with cumulative dose is presented below.

Table S9 and S10 give the variation with Carstairs quintile of the cumulative gamma-ray dose and radon exposure for cases and controls; for radon there is a clear tendency for more affluent groups to have higher exposures whereas no such trend is seen for gamma rays.

The correlation between radon concentration and gamma-ray dose rate is 0.09 ($P<0.001$); this is highly statistically significant because of the large numbers involved, but the correlation is not strong.

As shown in Table S11 the mean cumulative RBM equivalent dose from gamma rays and radon combined over the period from birth to diagnosis for the first controls is 4.0 mSv with a range from 0 (for those diagnosed at birth) up to about 31 mSv. On average, radon contributed about 10% of the RBM equivalent dose, although contributions were very variable with a range 1–80%.

Table 2 gives results for the main trend analysis using gamma-ray and radon exposures integrated from birth to diagnosis, with Carstairs quintiles included in the model. Significantly elevated excess relative risks (ERRs) were found for cumulative gamma-ray doses for total leukaemias (ICCC3 codes 11–15) (9% ERR per mGy; 95% CI 2, 17; $P=0.01$), lymphoid leukaemia (10% ERR per mGy; 95% CI 2, 19; $P=0.01$), and all cancers (3% ERR per mGy; 95% CI 0, 7; $P=0.04$). Lymphoid leukaemia is the largest component of the all leukaemias group (7267/9058 cases) and leukaemia makes up about one-third of all childhood cancers (9058/27 447 cases), and so these findings are not independent. There were no significantly raised risks of other types of childhood cancer. For the grouping of all childhood cancers excluding leukaemia the RR was raised (1.02), but the difference from 1.0 was far from being statistically significant. The radon RRs were elevated for several disease groupings, but none was close to statistical significance. Table 2 includes disease groupings of interest to the UK Committee On Medical Aspects of Radiation in the Environment.[34,35] The RRs per Carstairs quintile show the expected higher incidence of leukaemia in more affluent groups.[36]

The Figure 1 shows smoothed RR by cumulative gamma-ray dose group with fitted trend lines for all leukaemias combined and for all other cancers. There was a progressive increase in leukaemia ERR with dose: the excess was always positive, and statistically significant for doses >4.1 mGy. Although there were substantial uncertainties, the pattern for other cancers was somewhat different, with the ERR slightly and nonsignificantly negative up to about 12 mGy, above which there was a progressive non-significant increase in risk; because of the much greater leverage of the high-dose points this upturn at comparatively high dose resulted in an overall (nonsignificant) positive trend.

Table 3 gives results for leukaemia in terms of RR per mSv cumulative RBM equivalent dose. There was a 12% ERR (95% CI 3, 22; $P=0.01$) of total childhood leukaemia per mSv RBM dose from natural gamma radiation. Analyses were also carried out using estimates of combined (radon plus gamma ray) equivalent dose to the RBM. The results of this analysis were generally similar to the gamma ray results: for example, for all leukaemias 7% ERR per mSv (95% CI 1, 13; $P=0.02$).

Very similar results to the main analysis were obtained if alternative measures of SES rather than Carstairs quintile were used (Tables S12, S13), or if there was no modification by any measure of SES (Table S14); adjustment for SES appears to make little difference to the magnitude of the risk or its degree of statistical significance. For the analysis using social class based on (self-reported) father's occupation, the *P*-values were somewhat larger; this analysis included only 85% of the total

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Table 2. Trend analysis by childhood cancer diagnostic grouping

ICCC3 codes	*Diagnostic grouping*	*Number of cases*	*Number of controls*	*Relative risk*											
				Radon				*Gamma*				*Quintiles of carstairs index*			
				RR[a]	*95% CI*		P	*RR*[b]	*95% CI*		P	*RR*[c]	*95% CI*		P
11	Lymphoid leukaemia	7267	9571	1.24	0.94	1.64	0.13	**1.10**	1.02	1.19	0.01	**0.96**	0.93	0.98	0.001
12	Acute myeloid leukaemia	1316	1737	0.72	0.37	1.40	0.34	1.04	0.89	1.21	0.60	0.96	0.90	1.02	0.22
13–15	Other leukaemias	475	604	1.04	0.41	2.61	0.94	1.19	0.90	1.57	0.23	1.10	0.99	1.22	0.07
11–15	Total leukaemia	9058	11 912	1.12	0.88	1.43	0.35	**1.09**	1.02	1.17	0.01	**0.96**	0.94	0.99	0.002
21	Hodgkin lymphoma	939	1388	1.07	0.67	1.70	0.79	1.04	0.93	1.16	0.53	1.03	0.95	1.11	0.47
22	NHL	983	1302	1.29	0.69	2.39	0.43	1.04	0.89	1.21	0.61	1.07	1.00	1.16	0.06
21–25	Total lymphoma	2319	3274	1.14	0.80	1.62	0.47	1.01	0.93	1.09	0.86	1.04	1.00	1.09	0.08
11, 22	Lymphoid leukaemia + NHL	8250	10 873	1.24	0.96	1.60	0.10	**1.09**	1.02	1.16	0.02	**0.97**	0.95	0.99	0.01
11–15, 22	Total leukaemia + NHL	10 041	13 214	1.14	0.91	1.43	0.27	**1.08**	1.02	1.15	0.01	**0.97**	0.95	1.00	0.02
31–36	Brain and CNS tumours	6585	8997	1.15	0.88	1.50	0.32	1.02	0.96	1.09	0.49	0.98	0.95	1.01	0.14
41–122	Other malignant tumours	9485	12 610	0.99	0.80	1.23	0.95	1.02	0.96	1.08	0.57	0.98	0.96	1.01	0.19
21–122	All cancers except leukaemia	18 389	24 881	1.06	0.91	1.24	0.43	1.02	0.98	1.06	0.38	0.99	0.97	1.01	0.21
11–122	Total childhood cancer	27 447	36 793	1.08	0.95	1.23	0.25	**1.03**	1.00	1.07	0.04	**0.98**	0.97	0.99	0.01

Abbreviations: CI, confidence interval; CNS, central nervous system; NHL, non-Hodgkin lymphoma; RR, relative risk. Model includes cumulative radon exposure, cumulative gamma-ray exposure and quintiles of Carstairs index of deprivation. Exposure period taken as birth to diagnosis. RRs in bold are significantly different from 1.00 ($P<0.05$), RRs in bold and underlined are significantly different from 1 ($P<0.01$). [a]RR for each 10^3 Bq/m^{3}years increase in cumulative radon exposure. [b]RR for each mGy increase in cumulative gamma-ray exposure. [c]RR for each quintile increase on the Carstairs index of deprivation.

number of cases. Little difference resulted from analyses in which radon was excluded from the model (Table S15), or if attention was restricted to those case–control sets that had the most precise GridSquare/AP radon estimates (Table S16; this analysis included about 83% of the total number of cases and controls), or in which County District averages were used in place of HPA/BGS estimates for radon concentrations (Table S17).

An analysis was also undertaken considering radon concentration or gamma-ray dose rate as a measure of radiation exposure rather than cumulative exposure (Table S18). Most of the RRs were above unity, but none reached statistical significance under a two-sided test.

RRs for males were generally similar to those for females (for example, for total leukaemia 1.10 and 1.08 per mGy increase in cumulative gamma-ray exposure, respectively) (Table S19). For gamma rays, tests for heterogeneity between the sexes were not significant for any disease grouping listed.

Table S20 shows RR for leukaemia and for lymphoid leukaemia by single year of age at diagnosis. There is little pattern for radon exposure. The gamma-ray results show some pattern with attained age, but this should not be overinterpreted and formal tests for heterogeneity are not significant ($P>0.2$).

The main analysis uses exposure integrated from the date of birth to the date of diagnosis, roughly equivalent to the period from conception to diagnosis minus a latent period of 9 months. Other minimum latent periods (0, 12 and 24 months) were investigated, but no substantial changes were seen in RR, or in levels of statistical significance (Table S21; for latent periods of 12 and 24 months the analyses include about 96 and 85% of the total number of records, respectively).

Table S22 shows the results of an analysis analogous to the main analysis, but excluding second controls. This included 27 377 cases and the same number of controls, that is almost all the cases, but only about 74% of the total number of controls. The number of cases is lower than that in the main analysis because a few were matched to a second control only.

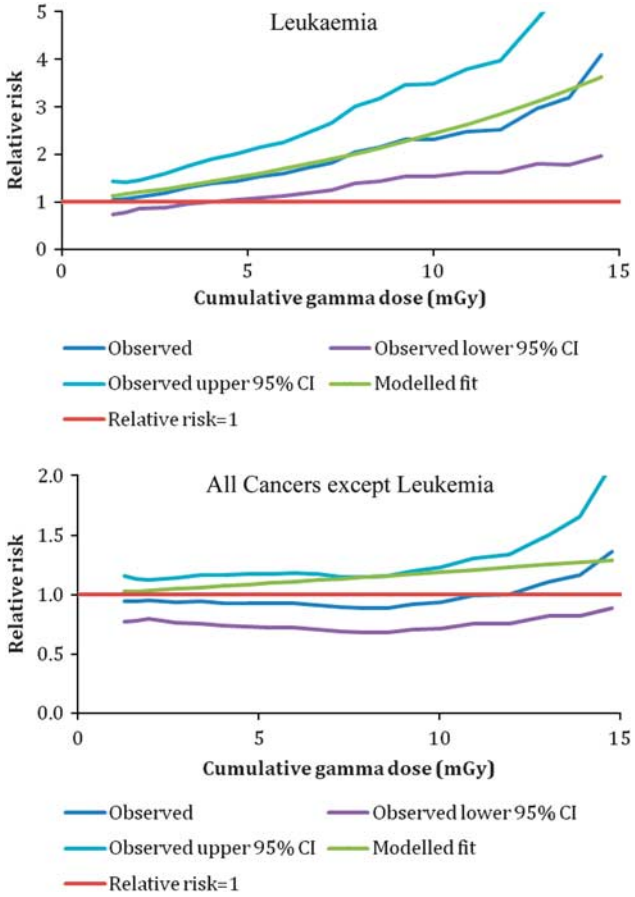

Figure 1. Observed (and 95% CI) and fitted relative risk for leukaemia (panel 1) and for all other cancers (panel 2) by cumulative gamma ray dose.

DISCUSSION

Our most striking finding was the statistically significant positive trend in the risk of childhood leukaemia with increasing dose of naturally occurring gamma radiation, of a magnitude comparable to that predicted by previous calculations based on standard risk and dose models. Excess risks were largely

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Table 3. Trend analysis for leukaemia and cumulative RBM equivalent doses from radon and gamma rays, separately and combined

	Relative risk per mSv for model containing gamma ray and radon RBM doses separately								*Relative risk per mSv for model including combined RBM doses from gamma rays and radon*			
	Radon				*Gamma*				*Gamma and radon*			
	RR[a]	*95% CI*		P	*RR*[b]	*95% CI*		P	*RR*[c]	*95% CI*		P
Lymphoid leukaemia	1.07	0.98	1.16	0.13	**1.13**	1.02	1.24	0.01	**1.09**	1.03	1.16	0.01
Acute myeloid leukaemia	0.91	0.75	1.10	0.34	1.05	0.87	1.28	0.60	0.98	0.86	1.11	0.74
Other leukaemias	1.01	0.77	1.33	0.94	1.25	0.87	1.78	0.23	1.09	0.89	1.34	0.40
Total leukaemia	1.03	0.96	1.11	0.35	**1.12**	1.03	1.22	0.01	**1.07**	1.01	1.13	0.02

Abbreviations: CI, confidence interval; RBM, red bone marrow; RR, relative risk. Model includes cumulative RBM equivalent dose (mSv) and quintiles of Carstairs index of deprivation. Exposure period taken as from birth to diagnosis. RRs in bold are significantly different from 1.00 ($P<0.05$). RRs in bold and underlined are significantly different from 1.00 ($P<0.01$). [a]RR for each mSv increase in RBM equivalent dose from radon. [b]RR for each mSv increase in RBM equivalent dose from gamma rays. [c]RR for each mSv increase in RBM equivalent dose from gamma rays and radon combined.

insensitive to adjustment for different measures of SES, to different estimates of radon exposure or to different assumed minimum latent periods.

The 95% CI on our leukaemia risk estimate is wide, but it is, nonetheless, instructive to compare the leukaemia risk that we observed with estimates derived from the Japanese atomic bomb survivors, who were exposed to higher acutely delivered doses. Table S23 shows that the cumulative leukaemia incidence risk at age 15 years predicted by the relative risk model derived here (and assuming 1 mSv per year to the RBM) is somewhat higher, at about 0.019%, than that predicted by the UNSCEAR 2006 models,[1] 0.010%, and by the BEIR VII models,[37] 0.007%. At attained ages greater than 4 years derived risks were higher than those predicted by both the UNSCEAR[1] and BEIR VII models[37]; at younger ages our derived risks were below those of UNSCEAR but higher than those of BEIR VII. However, given the substantial uncertainties in all estimates there is reasonable agreement between the risk predictions. These risks should be compared with the cumulative background risk of leukaemia incidence to age 15 years, which is around 0.06%.[17]

The results of the analysis using radon exposure rate or gamma-ray dose rate (Table S18) throw light on effects of exposures *in utero*, as the dose received during any antenatal period will be proportional to the radon concentration or gamma-ray dose rate. The dose received *in utero* will generally be smaller than the dose accumulated to diagnosis because the latter is usually incurred over a longer period. The results suggest that for leukaemia cumulative exposure (including the postnatal period) is the more important measure of exposure. The risk we derive in terms of cumulative RBM dose, 12% ERR per mSv (95% CI 3, 22), is similar to that obtained from the largest obstetric X-ray exposure study, 5.1% ERR per mGy (95% CI 2.8, 7.6).[38]

For types of childhood cancer other than leukaemia, no gamma-ray risk was elevated to an extent that approaches statistical significance (Table 2). We conclude that such risks, if they exist, are less than those of leukaemia. This is consistent with what is known about radiation-related risks for the typical cancers of childhood other than leukaemia: although the risks from antenatal exposure are similar to that for leukaemia, the risks from postnatal exposure are likely to be materially lower.[1,38] The power of our study to estimate the predicted risk of these other cancers was therefore markedly lower than that for estimating leukaemia risk.

A weaker (and statistically non-significant) association between childhood leukaemia and radon exposure was found in our study. This was what might be expected given the much lower assessed RBM doses from this source.[15] Our results were compatible with an association between childhood leukaemia and radon exposure of about the size that would be suggested by standard risk and dose calculations, and also with the results of studies reporting a positive association, in particular those of a recent case–control study of leukaemia and other childhood cancers in relation to radon exposure in Denmark.[39] However, the CIs on our RRs were wide enough for the results also to be consistent with no effect. For childhood cancers other than leukaemia, no significant associations with radon exposure were found.

A number of other case–control studies have investigated associations between natural background radiation and childhood cancer.[3,39,40] No consistent association has been found. However, power calculations[15] suggest that all previous case–control studies were underpowered (as were, to a lesser extent, geographical correlation studies). A power calculation using the methods of Little *et al*.[15] indicates that, after making allowance for cases and controls being assigned the same gamma-ray exposure rate, this study still has a power of about 50% to detect the predicted association between gamma-ray exposure and childhood leukaemia.

The study reported here considers only the gamma-ray and radon components of dose from natural background radiation; it does not assess the impact of the dose received from the ingestion of naturally occurring radionuclides in food and drink. Other sources of radiation exposure, in particular exposures incurred for medical reasons, are also omitted from our dose estimates, as it is not possible to assess these on an individual basis. It would not be expected that doses from these other sources of radiation would be significantly correlated with those from the exposures that are included, so their omission should not lead to the introduction of bias.

This study has considerable advantages: it is of exceptional size and the inclusion of almost all records from an essentially complete population-based register of cases (with previously matched controls) means that participation bias, so often a problem for case–control studies, does not arise. Indeed, it is difficult to envisage how a study encompassing the 10–20 000 study subjects required to achieve enough statistical power to stand a reasonable chance of detecting the predicted effect of natural background radiation upon the risk of childhood leukaemia could be other than record-based.

However, the absence of individual contact in the study carries with it the unavoidable disadvantage that radiation levels and SES variables have been estimated as the mean for an area including the maternal residence at the child's birth rather than being directly assessed for the homes of those concerned; in the case of the radon estimates, the areas were small, but for gamma rays they were County Districts. Inevitably, this leads to uncertainty in the exposure estimates. Further, the degree of geographical matching on the place of birth registration of cases and controls resulted in a proportion of radiation exposure rate estimates for the two being the same; this arose rarely for radon estimates, but approaching half of the cases had the same gamma-ray dose rate

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estimate as their controls. As the exposure period for controls was from birth to the date of diagnosis of the corresponding case, when a matched control is assigned the same dose rate as the case their cumulative doses will differ only because of small differences in the at-risk period arising from differences of up to 6 months in the dates of birth. This reduced the power of the study, but would not be expected to introduce bias. In this respect, it is reassuring that the effect of using higher resolution, rather than CD-averaged, radon measurements was to increase the RR for most endpoints, particularly for lymphoid leukaemia and all leukaemia (Tables 2, Table S17), suggesting that if there is any bias in the risks resulting from the use of CD-averaged gamma-ray measurements and consequent loss of case–control sets, it is towards the null. As indicated above, analyses using father's social class derived from his occupation as given on the birth certificate show very similar values of risk (Table S12) to those based on Carstairs index, if with slightly larger *P*-values; the larger *P*-values may arise, at least in part, because of the somewhat fewer records used.

A further consequence of the study design is that full residential histories for cases and controls were not available; address at birth was known for both cases and controls, but address at diagnosis only for cases. Consequently, cumulative radiation exposures were estimated on the basis of assessed exposure at the residential address at birth. About half the cases in this study had not moved between birth and diagnosis. This is broadly consistent with the findings of the UKCCS for controls[16] (no data for cases were given): 7629 families had lived at a total of 12 757 addresses (limited to addresses occupied for at least 6 months) so the mean number of addresses occupied was about 1.67, consistent with around half the controls not having moved, most of the remainder having moved once and a small proportion more often. The effect of study participants moving from the birth address will be to weaken the power of the study, but as it will introduce a Berkson-type error into the true dose, it would not be expected to introduce bias.[41] We note that the UKCCS set out to collect residential histories and conduct measurements at each address,[16] but finally analysed exposure data for the gamma-ray dose rate[13] and radon concentration[12] at a single address, that occupied at diagnosis. As we discuss in Supplementary Appendix 2, the sampling strategy for the gamma-ray survey is unlikely to appreciably bias results, and it seems unlikely that measurement error will result in significant dose-response bias.

The study has no information on potential confounders other than measures of SES, and the causes of the majority of cases of childhood leukaemia remain unknown. However, evidence is growing that infection has a major role in the aetiology of childhood leukaemia,[42,43] although it seems unlikely that such infections would be associated with higher naturally occurring gamma-ray exposures.

Ages at diagnosis are very similar for cases and their matched controls. However, if the distributions of these ages are considered for all cases and all controls then, on average, the controls are somewhat older than the cases (Table 1). This is due to the influence of the second controls (Table S2) and arises because cases born in, for example, 1990 can have a second control only if they are diagnosed at an age of 10 years or above. This will not affect the analysis, which is based on matched case–control sets. Nevertheless, we undertook a subsidiary analysis excluding second controls and this gave results very similar to the main analysis (Table S22), although the *P*-value for lymphoid leukaemia and gamma-ray dose is now below 0.01.

CONCLUSIONS

Many studies have tested for associations between childhood leukaemia and natural background radiation, but these generally lacked statistical power,[15] and many have suffered from other deficiencies. The present study is one of the few to have reasonable power of detecting the predicted risk of childhood leukaemia associated with natural background gamma-ray exposure. The statistically significant excess risk that is reported is around the level that would be predicted by recent analyses of moderate/high dose and high-dose rate data, and the study therefore supports the extrapolation of such risk models to protracted exposure to low doses or low dose rates. We found no strong evidence of excess risk of any other childhood cancer in relation to naturally occurring gamma radiation, nor for any childhood cancer with radon exposure. However, the statistical power of our study in relation to these other endpoints was low.

The possibility of confounding by some unidentified factor can never be entirely disproved, and is of particular concern when dealing, as here, with small RRs. However, we were unable to identify any mechanism whereby such confounding might plausibly account for the observed magnitude and specificity of effect in this study. Moreover, the study was of reasonable power and the findings conformed to prior predictions. Confirmation of our findings by similar studies in other countries where appropriately large cancer registration and dose databases are available would clearly be desirable, particularly in regions where natural background radiation levels are higher and more variable than in Great Britain.

We conclude that the significantly elevated RRs found in this study are likely to reflect a real effect on childhood leukaemia risk of exposure to natural background gamma radiation. Our study therefore provides support to the assumption that models of radiation-induced leukaemia risk derived from data observed at moderate and high doses and high dose rates may be appropriately applied to protracted RBM gamma-ray doses of about 1 mGy per annum. This is relevant to practical radiological protection in a number of situations, for example radiodiagnostic-imaging procedures.[44] The results of the study contradict the idea that there are no adverse radiation effects, or might even be beneficial effects, at these very low doses and dose-rates.

CONFLICT OF INTEREST

Dr Wakeford undertakes work as a paid consultant. All other authors declare no conflict of interest.

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