Report of a Record-based Case-control Study of Natural Background Radiation and Incidence of Childhood Cancer in Great Britain

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ABSTRACT

This is a record based case-control study to investigate associations between childhood cancer and natural background radiation. Cases and matched controls came from the National Registry of Childhood Tumours. Cases were cancers registered for children born and diagnosed in Great Britain during 1980-2006. 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 for radon. Among 27 447 cancer cases and 36 793 controls there was 12% excess relative risk (95% CI 3, 22; 2-sided p=0.01) of childhood leukaemia per millisievert of red-bone-marrow dose from gamma radiation; the association with radon was not significant. Associations for other childhood cancers were not significant for any radiation type. Excess risk was insensitive to alternative adjustments for socio-economic status.

The statistically significant leukaemia risk reported in this reasonably-powered study (power ~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 magnitude and specificity of the results. The association is therefore likely to be causal. Our results suggest that risks of childhood leukaemia apply at natural background levels of exposure at about the level extrapolated from high dose-rate data.

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EXECUTIVE SUMMARY

This report complements a published description (Kendall et al, 2012) of a record based case/control study that examines associations between childhood cancer and two components of natural background radiation: gamma rays (including the directly ionsing component of cosmic rays) and radon. Cases were all those on the National Registry of Childhood Tumours (NRCT) born and diagnosed with cancer or non-malignant brain tumours in Great Britain between 1980 and 2006 inclusive. One or two matched controls per case had been selected for the NRCT from the same birth register as the case. The study includes 27447 cases and 36793 controls.

Radon concentrations and gamma ray dose rates were estimated for cases and controls on the basis of the mother's place of residence at the time of the child's birth. Gamma ray exposures were estimated as the average for the County District (CD) in question and radon exposures were estimated from a predictive map based on geological boundaries and radon in house measurements. Slightly different types of radon mapping were available depending on the precision with which the birth address was known and on the degree of detail in the mapping for the area in question. Subsidiary analyses included only case/control sets where all members had the most reliable grade of radon measurement and also used as measure of exposure the mean radon concentrations in CDs (the radon analogues of the gamma-ray estimates).

The main analyses use measured gamma-ray dose-rate and radon activity concentration integrated from birth to diagnosis (approximating the period from conception to nine months before diagnosis). These quantities are proportional to tissue doses from the two components separately. To compare the risk estimates from this study with published values, it is necessary to estimate 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. Analyses were also undertaken using the radon concentration or gamma-ray dose rate which are measures of the rate at which exposure is incurred. These analyses also give information on the importance of the doses incurred in the antenatal period.

Socioeconomic status is found to affect rates of childhood cancer in the UK and the Carstairs index of Social Deprivation was included in the main analysis. The father's social class, derived from the occupation given on the birth certificate was used in a subsidiary analysis.

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 exposures.

A power calculation, making allowance for cases and controls being assigned the same gamma-ray exposure rate, indicates that this study has a power of about 50% to detect an association between gamma-ray exposure and childhood leukaemia.

In the pre-specified main analysis, elevated odds ratios were found for time integrated radon and gamma ray exposures and a number of disease groupings. Those for gamma rays and lymphoid leukaemia, total leukaemia and all childhood cancers reached statistical significance. Two other disease groupings dominated by lymphoid leukaemia were similarly significant. In terms of the dose to red bone marrow, there was 12% excess relative risk (95% CI 3, 22; 2-sided p=0.01) of childhood leukaemia per millisievert of red-bone-marrow dose from gamma radiation; the association with radon was not significant. Associations for other childhood cancers were not significant for any radiation type.

Subsidiary analyses gave a similar qualitative picture but the odds ratios were generally less significant. Some of the subsidiary analyses included fewer records which is likely to account, at least in part, for the reduced significance.

This study has the disadvantage compared to conventional case/control studies of lacking individual measurements of radiation exposure or of potential confounding factors for study participants. The partial geographical matching on the place of birth of cases and controls results in approaching half of the cases having the same gamma-ray estimate as their controls. This reduces the power of the study, but would not be expected to introduce bias.

However, this study is free of participation bias which can be a serious problem when individual consents are required. It is also very much larger than the practical maximum for conventional (interview-based) case-control studies, having an order of magnitude more cases and controls than the UK Childhood Cancer Study.

The statistically significant association that we have found between natural gamma rays and childhood leukaemia is consistent with high dose-rate predictions from data on survivors of the atomic bombs. Substantial bias is unlikely, and we cannot identify mechanisms by which confounding might plausibly account for the observed magnitude and specificity of the results. The association is therefore likely to be causal. Our results suggest that risks of childhood leukaemia apply at natural background levels of exposure at about the level extrapolated from high dose-rate data.

CONTENTS

1 INTRODUCTION

1.1 Naturally occurring radiation sources and exposures

Ionising radiation from natural background sources is ubiquitous in the environment. There are three such sources:

Very long lived naturally produced radionuclides (e.g. U-238, Th-232 and K-40) incorporated into the material of the Earth when it was formed, and their radioactive decay products,

Cosmic rays from the sun or more distance sources, and

Radionuclides (such as C-14 and H-3) formed by interactions of cosmic rays with nucleii in the upper atmosphere.

People receive radiation doses from ingestion of naturally occurring radionuclides in food and drink and inhalation of natural radioactive materials. Inhalation is normally of lower radiological significance than ingestion with the important exception of doses from isotopes of the naturally occurring radioactive gas radon and their decay products. Two isotopes of radon are normally important, Rn-222 and Rn-220; the latter is often known as “thoron” because it is derived from thorium-232, and it is generally less important than Rn-222, derived from uranium-238. Isotopes of radon and their decay products deliver most of their dose to parts of the lung and have been shown to cause lung cancer in adults (Darby *et al.* 2005; Krewski *et al.* 2005; Lubin *et al.* 2004), but they are less important as a cause of cancer in childhood. In addition to direct ingestion and inhalation, radionuclides present in a pregnant woman can be transferred to the embryo and fetus.

Radionuclides in the environment can deliver dose from external gamma rays as well as when they are ingested or inhaled. Most of the dose from external gamma rays is delivered in buildings; both construction materials and the ground contribute to this dose. Dose rates from gamma rays inside buildings are about twice those outside and the average person spends much more time in buildings than outside (Wrixon *et al.* 1998). A large fraction of cosmic rays is absorbed in the atmosphere, but some deliver dose at ground level. Most of the cosmic rays at ground level are directly ionising particles, predominantly muons, but a proportion are neutrons.

These naturally occurring sources may emit radiations of different types. Broadly speaking these radiations can be divided into high and low Linear Energy Transfer (LET) fractions. The low LET component is sparsely ionising and is mainly composed of penetrating γ-rays delivering roughly similar doses to all organs and tissues. The high LET component is densely ionising and is mainly composed of short-ranged α-particles delivering doses to different organs and tissues that differ considerably, depending on how much α-particle-emitting radioactive material is present in, or adjacent to, the organ or tissue. High and low LET radiations differ in their ability to cause biological damage of relevance to stochastic health effects, and this is quantified for radiological protection purposes by the use of equivalent dose, which consists of the

radiation absorbed dose multiplied by a LET-dependent radiation weighting factor broadly corresponding to the ability of the radiation type to cause relevant biological damage. For low LET radiation the radiation weighting factor is one; for high LET α-particles it is 20.

A further complication is that ingested or inhaled radionuclides do not deliver their doses instantaneously but will continue to irradiate the body until the material has decayed away or been eliminated from the body by biological processes. The pattern of deposition of radioactive materials in different body organs and tissues and the rate at which they are excreted depends on the chemical nature of the material and on the age of the individual. For radiation protection purposes protracted doses are summarised as the committed dose: the dose that will be incurred up to age 70 years, or in the 50 years following intake in the case of adults.

The effective dose is a radiation protection quantity designed to give a detriment-weighted measure of the overall risk of stochastic health effects caused by any particular pattern of radiation exposure across the body. It consists of a weighted sum of committed equivalent organ or tissue doses. The tissue weighting factors are designed to be proportional to the sensitivity of the tissue in question to radiation-induced stochastic health effects, weighted by the detriment of the effect. Published data on radiation exposure of population groups is often expressed in terms of effective dose.

Table 1.1 gives the contributions to the effective dose received by a ten-year old child from the different components of natural radiation. This provides a general indication of the relative importance of the different contributions. However, it is clear that in order to get a proper understanding of the radiation risk to any particular organ or tissue it is necessary to consider dose to the organ or tissue in question rather than the effective dose. It is also necessary to consider the actual doses delivered at specific times after intake rather than the committed doses. For a particular radiation-induced disease it is also desirable to use a specific Relative Biological Effectiveness (RBE) rather than a generic radiation weighting factor for combining low and high LET doses; however, information on RBE for particular endpoints is very often lacking. Moreover, as discussed below, for many childhood cancers it is either not clear which are the target tissues or else there are no generally accepted models for estimating the relevant doses.

It is to be expected that all the components of radiation from natural sources will contribute to some extent to radiation damage in general, and particularly to cellular modifications of relevance to the induction of cancer in children. However, it is generally not practicable to include all of them in epidemiological studies. The components that can be studied directly are terrestrial gamma rays combined with the directly ionising component of cosmic rays, and radon and its decay products.

The other main sources of exposure are thoron, cosmic ray neutrons and radionuclides in food (Table 1.1). Thoron is less easy to measure than radon and many fewer measurements of thoron concentrations in homes have been made. However, all the indications are that thoron doses are lower than those from radon (Kendall and Phipps 2007). The measurement of doses from cosmic ray neutrons requires complex and

expensive equipment and would be quite impractical on an individual basis. Doses from food are much the largest of the contributions considered here. If detailed information were available on the quantities of different type of foodstuff eaten by an individual and on the concentration of different radionuclides within them then it would be reasonably straightforward to estimate the resulting tissue doses, to within the accuracy of the biokinetic and dosimetric models. However, information on` individual diets is rarely collected. Moreover, food is now obtained from a far-flung and changing variety of sources so that radionuclide concentrations are difficult to predict.

As noted above, the relationship between the measured radiation quantities and the doses to tissues in which specific types of childhood cancer originate is not simple. However, since both of the measured components of radiation deliver doses that are essentially instantaneous (unlike long-lived radionuclides in food and drink) the dose to sensitive tissues from each type of radiation separately can be taken to be proportional to the measured quantities. In principle, some increased study power will result from considering the dose to the specific target tissue from both components of radiation combined, but this is dependent on adequate methods for estimating the relevant tissue dose.

1.2 Calculations of doses to organs from natural radiation

A number of investigations into doses from natural radiation sources have been carried out e.g. by Watson et al (Watson *et al.* 2005) and Kendall et al (Kendall *et al.* 2006). In the present context, particular attention concentrates on those components of natural radiation exposure that can be measured in epidemiological studies: gamma rays (with the directly ionising component of cosmic rays) and radon-222 and its decay products.

Doses to different organs from penetrating gamma rays typically differ by up to a few tens of percent. However, radon delivers most of its dose in the form of short-ranged high LET alpha particles and doses to different organs differ very considerably. Most of the dose from radon is received by the respiratory tract and, under typical UK conditions, equivalent doses from radon to organs and tissues outside the respiratory tract are generally lower than those from terrestrial gamma rays.

An important question is the identity of the target tissues for the induction of different types of childhood cancer by radiation. About one third of childhood cancers are leukaemias, about one third tumours of the CNS or peripheral nerve cells and the remaining one third are of various other types, with lymphomas the largest single group (about 9% of the total) (Stiller 2007). Leukaemias are known to be induced by radiation and it is believed that the red bone marrow is the tissue in which these diseases arise, at least in the late fetus and after birth. It may be a plausible assumption that cancers of other organs and tissues are caused by irradiation of the organ or tissue in question. However, with few exceptions, models for calculating these doses from radionuclides within the body are not available. This applies in particular to radon which delivers most of its dose from very short ranged particles.

Simmonds et al 1995 (Simmonds *et al.* 1995) in their study of the risks of radiation-induced leukaemia and non-Hodgkin's lymphoma considered the question of doses to

the lymphatic system as well as those to red bone marrow. They noted that lymphatic tissue is present in varying proportions in many organs and tissues, but that techniques for estimating doses to the lymphatic system as a whole were not available. However, they identified a number of tissues which accounted for a substantial fraction of the total lymphatic system in the body: lymph nodes (both thoracic and extrathoracic), liver, spleen, kidneys, pancreas, uterus, thymus, thyroid, stomach, small intestine, upper large intestine, lower large intestine, RBM and bone surfaces. Simmonds et al went on to calculate the mass-averaged dose to this set of tissues as the best available estimate of dose to the lymphatic system. Little et al (Little *et al.* 2009) updated the calculation of dose to the set of organs specified by Simmonds et al using more recent dosimetric modelling, but Little et al did not go so far as to calculate a single summary dose to the lymphatic system. They drew attention to the difficulties in estimating doses to lymphatic tissue using models which yielded only mean doses to organs which contained variable proportions of lymphatic tissues, particularly since the lymphatic tissue was likely to be inhomogeneously distributed within the organ. Harrison (Harrison 2010) agreed that the estimation of the relevant quantity was fraught with difficulty.

Dosimetric and modelling studies have therefore tended to focus on leukaemia and on RBM as the target tissue. As noted above, RBM equivalent doses from terrestrial gamma rays are normally larger than those from radon. Detailed investigations of RBM dose have been carried out (Kendall *et al.* 2009). Table 1.1 also shows the mean annual RBM doses from conception to the fifteenth birthday. For penetrating radiation the contributions to RBM dose are similar to the effective doses, whereas those from ingested radionuclides are rather larger than the contributions to effective dose. However, the annual RBM dose from the inhalation of radon and thoron is very much smaller than the annual effective dose, because the latter is dominated by the relatively large dose to lung.

1.3 Radiation-induced cancer in children

In this section we give a brief summary of the evidence concerning the induction by ionising radiation of leukaemia and other cancers in children. This may be a consequence of irradiation *in utero* (i.e. exposure while in the womb) or after birth. Such irradiation may also result in a risk of cancer after the childhood years (conventionally taken as before the fifteenth birthday), but this is not the focus of the present discussion. A suggestion that exposure to radiation of parents before the conception of their children may materially increase the risk of childhood leukaemia has not been confirmed and the idea has now effectively been abandoned (COMARE 2002), and so will not be discussed further here.

1.3.1 Postnatal irradiation

Studies of the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki in 1945 show clearly that irradiation of children leads to a marked increase in the risk of leukaemia, which manifests itself both in the childhood years and in later life (Delongchamp *et al.* 1997; Preston *et al.* 2008; Preston *et al.* 2004; UNSCEAR 2008).

Although the evidence for an increase in the risk of cancers other than leukaemia among the Japanese atomic bomb survivors in adult life is beyond dispute, with the exception of childhood leukaemia no childhood cancer was recorded among the survivors who were irradiated after birth. However, the follow-up of solid tumours amongst the atomic bomb survivors did not start until 1950 for mortality and 1958 for incidence, so some cases may have been missed. Nonetheless, it is apparent that any risk of childhood cancers other than leukaemia among the Japanese atomic bomb survivors exposed postnatally is much less than that for leukaemia (Wakeford and Little 2003).

Studies of children exposed postnatally for diagnostic or therapeutic reasons indicate that leukaemia and solid cancers can be induced (Haddy *et al.* 2006; Little 2008; Tucker *et al.* 1988; UNSCEAR 2008). However, evidence that this childhood irradiation gives rise to increased rates of cancer before age 15 years is more scanty; investigators have understandably not regarded as a priority the question of whether second cancers arise before or after the somewhat arbitrary division at the age of 15 years.

A notable exception is increased thyroid cancer among those irradiated in infancy because of an enlarged thymus (Shore *et al.* 1993). Neglia et al (Neglia *et al.* 2006) reported an increase of CNS tumours in children who received radiotherapy for a first cancer; there was a strong suggestion of gliomas appearing before age 15 years. Rajaraman et al (Rajaraman *et al.* 2011) analysed data from the UK Childhood Cancer Study on children who had been exposed to diagnostic radiation in the first 100 days of life. A statistically significant excess of lymphomas was found, but the authors were cautious in the interpretation of this finding. In contrast, Hammer et al (Hammer *et al.* 2009) in a cohort study of about 93000 children who had undergone diagnostic radiology found no evidence for increased levels of malignancy. However, they noted that their results were consistent with a broad range of risks. In summary, while there is evidence that postnatal therapeutic irradiation induces thyroid and CNS cancers, it is probably safe to conclude that in most instances radiation-induced cancers of other types before age 15 years are rare.

A substantial increase in thyroid cancer before age 15 years has also been observed among those highly exposed as children to radioiodine in areas of the former USSR heavily contaminated by releases from the Chernobyl accident (UNSCEAR 2008). Variations in the efficiency of screening may explain part of the excess but much of it is associated with high radiation doses to the thyroid resulting from radioisotopes of iodine released during the accident. The thyroid cancer risk coefficients that may be derived from children exposed to radioiodine as a consequence of the Chernobyl accident are broadly compatible with estimates that may be obtained from children exposed to external sources of radiation (Ron *et al.* 1995).

There is plausible evidence that therapeutic irradiation of children with the heritable form of retinoblastoma causes the subsequent development of second primary tumours (SPT) under the age of 15 years. In one of the few cohorts of such children studied (MacCarthy *et al.* 2009) high rates of SPT were seen. Twenty six out of 100 of all SPT occurring before age 50 years did so within childhood, and for osteosarcomas the proportion occurring in childhood was particularly notable, at 18 out of 31. The rates per 100,000 person-years of follow-up were 166 and 33 for all SPT and osteosarcoma

respectivley in the 0-4 years age group and 349 and 283 in the 5-14 years age group. Most children in this cohort with heritable retinoblastoma would have received therapeutic irradiation, but it is not stated how many of the SPT occurred within the irradiation field. These children have a genetic constitution which might render them unusually sensitive to irradiation, but it seems that therapeutic irradiation doses can cause further childhood cancers of different types.

In summary, while there is evidence that postnatal therapeutic irradiation induces thyroid and CNS cancers, it is probably safe to conclude that in most instances radiation-induced cancers of other types before age 15 years are rare in children without some genetic predisposition.

1.3.2 Antenatal irradiation

As well as the induction of cancers by postnatal irradiation, there is evidence that irradiation *in utero* leads to an increased risk of childhood leukaemia. However, unlike the often equivocal evidence relating to exposure to radiation after birth, there is evidence that exposure *in utero* leads to an increased risk of cancers other than leukaemia in childhood, and that the excess relative risk of these other childhood cancers is around the same level as that for leukaemia. This evidence came originally from the Oxford Survey of Childhood Cancers (OSCC), a nationwide case-control study of childhood cancer mortality in Britain that investigated, inter alia, the effects of radiographic examination of the abdomen of pregnant women (Stewart *et al.* 1956; Stewart *et al.* 1958), but the association has since been supported by many other case-control studies in various countries (Bithell 1992; Doll and Wakeford 1997; Wakeford 2008). Accurate estimates were generally lacking for the radiation doses involved in obstetric radiography and consequently there is less certainty about the risks per unit fetal dose indicated by these studies. However, it has been shown (Wakeford and Little 2003) that the relative risk coefficient for leukaemia obtained from the OSCC is compatible with that obtained from the Japanese atomic bomb survivors irradiated after birth.

There were no recorded cases of leukaemia in the offspring of Japanese mothers irradiated at Hiroshima and Nagasaki while they were pregnant, but the expected number of cases in the absence of any effect of radiation was low (~0.2); although there appears to have been follow-up for mortality before October 1950 (Yoshimoto *et al.* 1988) most analyses (Yoshimoto *et al.* 1998, 1994, Delongchamp *et al*. 1997) utilise mortality follow-up starting then, possibly because of incompleteness in follow-up in the early post-war period. It is impossible to know whether deaths from leukaemia might have been ascribed to infectious diseases in the period before October 1950 – there are no deaths from this cause, or any other malignancy, in the *in utero* cohort in the period August 1945-September 1950 (Yoshimoto *et al.* 1988). Moreover, studies of chromosome aberrations among those exposed *in utero* suggest that the fetal haematopoietic system is particularly sensitive to cell killing by moderate doses of radiation, which could contribute to the absence of leukaemia among the intrauterine exposed bomb survivors (Nakano *et al.* 2007; Ohtaki *et al.* 2004).

Studies of antenatal radiography generally suggest that, within the significant uncertainties, the risks of irradiation *in utero* are similar for induction of leukaemia and of other childhood cancers (Bithell and Stewart 1975; Doll and Wakeford 1997; Monson and MacMahon 1984). This contrasts with the evidence for an absence of a significant excess risk of the typical cancers of childhood other than leukaemia following postnatal irradiation. Further, there were two childhood solid tumours in the atomic bomb survivors irradiated *in utero* when only 0.28 were expected (Wakeford and Little 2003), an excess that is statistically significant. This suggests that childhood leukaemia may be induced by exposure to radiation both *in utero* and after birth, whereas the common cancers of childhood other than leukaemia can be induced by irradiation *in utero* (at much the same level of risk as leukaemia), but at a much reduced level by irradiation after birth, if at all.

1.3.3 Summary

In summary, there is evidence for an excess of childhood leukaemia following irradiation *in utero* or in the childhood years. There is also evidence for an excess of childhood cancers other than leukaemia following irradiation *in utero*, at about the same excess relative risk (proportional increase) as for leukaemia. However, there is less evidence for an excess of childhood cancers other than leukaemia following irradiation after birth, with the exception of thyroid cancer, which is rare in children, and gliomas following high doses from radiotherapy.

1.4 Risks of radiation exposure at low doses

Direct evidence on radiation risks to people comes from epidemiological studies, notably of survivors of the atomic bombings of Hiroshima and Nagasaki. However, at low doses these epidemiological studies inevitably suffer from problems of insufficient statistical power, and biases and confounding present greater difficulties to interpretation when the predicted effects of exposure are small. Judgements about extrapolation from information obtained from moderate and high levels of exposure to lower doses are made in the light of information from cellular studies and animal experiments that provide radiobiological insights into the basic underlying mechanisms of radiation interaction with living cells and organisms. Radiation risks are reviewed by international organizations, such as the International Commission on Radiological Protection (ICRP) and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), and the consensus of these bodies (International Commission on Radiological Protection 2008; UNSCEAR 2008) is that the most appropriate risk model at low doses or low dose-rates is one in which the risk of radiation-induced cancer is assumed to increase in direct proportion to increasing radiation dose, with no threshold. Any increment of exposure above natural background levels will produce a linear increment of risk (the so-called linear no-threshold (LNT) model). It is, of course not implausible that the biological response to low doses is different from that at high doses. However, the evidence to distinguish such differences is generally not available.

The present study offers the prospect of direct evidence on the effect of environmental levels of radiation exposure upon the risk of childhood cancers.

1.5 Calculations of the induction of childhood leukaemia by natural radiation

A review of radiation exposures from natural and anthropogenic sources was carried out in the context of COMARE's investigation of levels of childhood cancer in Cumbria (COMARE 1996; Simmonds *et al* 1995). Age dependent doses to the red bone marrow of children and young people from natural radiation sources were estimated and models of radiation risks (NRPB 1993) were used to calculate the predicted number of radiation-induced cancers. COMARE concluded that about a third of leukaemia in young people aged up to 25 years is attributable to natural background radiation.

Recently, the doses to the red bone marrow have been reassessed using more recent dosimetric and biokinetic models than those available to COMARE (Kendall and Fell 2011; Kendall *et al* 2009). The average annual equivalent dose to the RBM of a British child has been calculated as ~1.4 mSv (see Table 1.1). These dose estimates and recent models for the induction of leukaemia by radiation (National Research Council (NRC) 2006; UNSCEAR 2008) were used to calculate the number and proportion of leukaemias predicted to be caused by natural background radiation in Great Britain (Kendall *et al.* 2011; Little *et al* 2009; Wakeford *et al.* 2009). There are considerable uncertainties in these calculations, not all of which are easy to quantify. However, the more recent calculations support the conclusion of COMARE that a significant fraction of leukaemia in children and young people is likely to be caused by natural radiation, though the predicted attributable fractions are rather lower in the more recent calculations, which suggest that some 15% of childhood leukemia cases in Britain may be attributable to natural background radiation (about one half to one third of the fraction estimated by COMARE).

Little et al also used information on the distribution of radon and gamma ray exposures to examine the statistical power of epidemiological studies of childhood leukaemia and these types of naturally occurring radiation in the UK (Little *et al.* 2010). Their calculations suggested that the number of cases of childhood leukemia required to achieve 80% power to detect the predicted increase in the risk produced by these sources of radiation exposure using a one-sided 5% test would be:

For a cohort study: 6400 cases

For a case/control study with 5 controls per case: 7800 cases

For a case/control study with 1 control per case: 12800 cases

For a geographical correlation study: 8700 cases

These estimates assume that doses from radon and gamma rays (including the directly ionizing component of cosmic rays) are combined. For studies using gamma rays alone, the required numbers of cases would be somewhat larger, and for radon alone much larger, to achieve the same degree of power.

Little et al argued that most previous studies had been underpowered and that many were subject to unquantifiable biases and confounding. Nonetheless, large studies should be capable of detecting the predicted risk of childhood leukemia from natural

background radiation and potentially provide important evidence on the risk of childhood leukemia after protracted low-level irradiation.

1.6 Previous epidemiological studies of natural radiation and childhood cancer

A number of epidemiological studies have been conducted to investigate the possibility of a link between childhood cancers, in particular leukaemia, and exposure to ionising radiation from natural sources (see Appendix A for a description of some of these studies). These have been of case-control or geographical correlation ("ecological") design – cohort studies of an uncommon disease such as childhood cancer are impracticable.

Case-control studies allow a greater range of data to be collected, and these relate to the individual rather than to groups. However, they are complex and expensive to conduct and may therefore be limited in size. They may also be subject to systematic errors, such as selection bias (in which those cases and controls enrolled into the study are not fully typical of the spectrum of potential cases and controls), participation bias (in which a different level of participation in the study between cases and controls may distort the findings), and information bias, e.g. recall bias, (in which the accuracy of the information supplied differs between cases and controls).

Geographical correlation studies are relatively cheap and quick to conduct and are typically larger than case-control studies, so they are potentially the most powerful type of practicable study. However, they lack individual measurements of the risk factor being examined or of potential confounding factors, and are liable to "ecological bias", when associations at the group level do not reflect associations at the individual level. This was illustrated by a negative association between average domestic radon exposure and lung cancer mortality rate for US counties (Cohen 2000), contrasting with the positive association found in case-control studies of residential radon exposure and lung cancer (Darby *et al* 2005). The extent of the ecological bias in Cohen's analysis was demonstrated by Puskin (Puskin 2003) who showed that there were similar negative correlations for various smoking related endpoints; there were much weaker correlations for cancers only weakly related, or unrelated, to smoking. Lagarde and Pershagen (Lagarde and Pershagen 1999) also demonstrated the dangers of ecological analysis, reanalysing the Swedish residential radon case-control study as if it were an ecological study, as a result of which the positive trend became negative. However, geographical correlation studies are most vulnerable when there is a powerful individual risk factor (as with smoking and lung cancer); no such powerful risk factor is known for childhood leukaemia or other childhood cancers, although a major, presently unidentified, factor (such as an infectious agent affecting childhood leukaemia) cannot be ruled out.

One of the largest of the case-control studies was carried out in the United Kingdom under the auspices of the UK Coordinating Committee on Cancer Research. This UK Childhood Cancer Study (UKCCS) included a total of 3838 cases of childhood cancer and 7629 controls (UK Childhood Cancer Study Investigators 2000). However, the

analyses for natural sources of radiation were substantially smaller: the radon part of this study included 2226 cases (of which 951 were leukaemias) and 3773 controls (UK Childhood Cancer Study Investigators 2002a), while the gamma ray analysis included 2165 cases and 5096 controls (UK Childhood Cancer Study Investigators 2002b). As the authors of the UKCCS acknowledge, the study was subject to considerable participation bias and the findings for radon in particular were dominated by this bias (Law *et al.* 2002).

Raaschou-Nielsen et al conducted a record-based nationwide case-control study of childhood cancer in Denmark (Raaschou-Nielsen *et al.* 2008). The study included 1153 cases of leukemia (2 controls per case), 922 central nervous system tumors (3 controls per case) , and 325 malignant lymphomas (5 controls per case) identified from the Danish Cancer Registry. Radon concentrations were estimated using a predictive method developed by Andersen et al (Andersen *et al.* 2007) which takes account of the local geology and the construction details of the house. Radon levels in residences of children and the cumulative exposure of each child were calculated as the product of exposure level and time, for each address occupied during childhood. Children were divided into three exposure groups of accumulated radon exposure. Cumulative radon exposure was associated with risk for acute lymphoblastic leukemia (ALL): a linear dose-response analysis showed a 56% increase in the rate of ALL per 10^3 Bq/m^3-years increase in exposure, although the confidence interval is wide. No association was found with the other types of childhood cancer. This study was entirely record based and was therefore free of bias due to incomplete participation or any other obvious source. The authors suggest that domestic radon exposure increases the risk for ALL during childhood and that about that 9% of childhood ALL in Denmark may be attributable to radon. However, the confidence interval for this fraction is wide (the lower confidence limit is <1%) and the results are compatible with the predictions of conventional modelling.

Other case-control studies of radon and childhood cancer have failed to demonstrate a convincing association and reviews have concluded that any association is weak (Laurier *et al.* 2001; Raaschou-Nielsen 2008). These findings for childhood leukaemia are consistent with the power calculations reported above which suggest that previous case-control studies have been far too small to detect an association of the expected size between childhood leukaemia and natural radiation exposure.

A number of geographical correlation studies have suggested an association between radon exposure and childhood cancers of various types (Alexander *et al.* 1990) for acute lymphoblastic leukaemia (ALL); Gillman and Knox, (Gilman and Knox 1995) for all cancers and solid cancers; Evrard, (Evrard *et al.* 2005) for acute myeloid leukaemia (AML); Thorne et al, (Thorne *et al.* 1996) for AML). A review of geographical correlation studies of childhood leukaemia and domestic radon exposure (Raaschou-Nielsen 2008) found a “consistent pattern of higher incidence and mortality rates for childhood leukaemia in areas with higher average indoor radon concentrations”, although as noted above this pattern is much less obvious in case-control studies, and may be a reflection of uncontrolled confounding present through the use of group averages rather than individually based data (see above). Two nationwide geographical correlation studies of childhood leukaemia and background gamma radiation have been conducted in

France and Great Britain (Evrard *et al* 2005; Richardson *et al.* 1995). Neither study found an association. Richardson et al (Richardson *et al* 1995) showed that it is important to adjust for other factors in such studies, in particular socio-economic status, although adequate adjustment may be difficult if groups based on large areas are involved. Geographical correlation studies have generally been too small to have sufficient power to detect the predicted effect, though less so than case-control studies. (Laurier *et al* 2001; Raaschou-Nielsen 2008).

Geographical correlation studies suffer from severe interpretational problems because they are based on group averages. On the other hand, case-control studies requiring individual consent are subject to (possibly large) participation bias and are likely to be extremely expensive if an adequate number of cases is to be included. Record-based case-control studies avoid these problems, though they are not free of difficulty (in particular in that individual doses have to be estimated rather than measured).

1.7 The present study

As noted above the record-based case-control design avoids a number of potential sources of bias: if cases and controls are drawn from pre-existing registers and if no contact is made with individual study participants then participation bias is avoided and other major sources of bias (e.g. selection and information) should be minimised. This is, of course, at the cost of losing the possibility of individual radiation measurements in the homes of study participants and of gathering information about potential confounding factors on an individual basis.

Accordingly, the present study is of case-control design, both cases and controls being drawn from the National Register of Childhood Tumours. This is an essentially complete collection of all cancers arising in children born and diagnosed in Great Britain over the period of the study together with one or two matched controls per case (Kroll *et al.* 2011a; Stiller 2007). The numbers of controls (and the availability of residential address data) were dictated by reasons unrelated to the present study. The study is record based and no contact was made or interviews conducted with study participants. Information on exposures to terrestrial gamma rays (with the directly ionising component of cosmic rays) was obtained from the results of a National Survey (Kendall *et al* 2006; Wrixon *et al* 1998). Estimates of exposures to the natural radioactive gas radon were made using a detailed predictive system based on many measurements of radon concentrations in houses and on geological boundaries (Miles and Appleton 2005). This has the significant disadvantage that the assessments of radiation exposures are the estimated mean values for areas including the addresses of the study participants rather than being direct measurements in the houses concerned, but in our view this is more than compensated by advantages arising from the avoidance of potential sources of bias that have seriously affected previous case-control studies. Moreover, the study is much larger (i.e. much more powerful) than would be practicable for a case-control study using measurements of individual exposures, being more than ten times larger than the UKCCS.

Socio-economic status (SES) affects childhood cancer rates in the UK (COMARE 2006; Kroll *et al.* 2011b) and allowance is made for this factor using the small area census based Carstairs Index. An alternative indicator of SES can be obtained from the father's occupation as stated on the birth certificate. This relates to the individual rather than to the small area of residence, but it is based on self-reported information and is incomplete. These measures of SES are used to adjust for the influence of SES when examining the effects of natural background radiation upon the risk of childhood cancer.

The present study has the considerable advantage of following an estimation of the predicted risk of childhood leukaemia arising from natural sources of radiation based upon the most recent leukaemia risk models and the distribution of RBM doses within the British population of children. (Little *et al* 2009; Wakeford *et al* 2009). Further, there has also been an investigation, using the same risk models and RBM dose estimates, of the size of various types of epidemiological study that would be required to have a reasonable chance of detecting the predicted risk of childhood leukaemia produced by natural background radiation. (Little *et al* 2010)

These statistical power calculations, as they relate to a nationwide case-control study such as the one reported here, provide a material contribution to an accurate interpretation of any statistically significant associations found between the risk of childhood leukaemia and the doses of radiation received from natural sources, which is often absent from other studies; as we show in the Discussion, the power calculations demonstrate that the present study has reasonable power to detect the predicted effect on childhood leukaemia risk. The difficulties in interpreting results from severely underpowered studies are illustrated by Land (Land 1980), who showed that if by chance such a study were to generate a statistically significant result then the point estimate of the risk was likely to be markedly higher than its true value. A statistically significant result from a materially underpowered study may also mean that confounding and/or bias are playing a substantial role in the study.

Although similar assessments have not been performed for childhood cancers other than leukaemia, from the discussion above it will be inferred that radiation exposure after birth is unlikely to generate a risk of these other childhood cancers that is as large as that for leukaemia (with the exception of thyroid cancer, which is rare in childhood). Therefore, it would be anticipated that the risk of childhood cancers other than leukaemia is influenced to a much lesser extent by natural background radiation than the risk of childhood leukaemia, with only exposure *in utero* likely to make a material contribution to the radiation-induced risk of these other childhood cancers.

This background information greatly strengthens the interpretation of the results of this study in that there is a prior expectation of a realistic chance of detecting the predicted influence of radiation from natural sources upon the risk of childhood leukaemia (most of which arises from exposure to gamma-rays rather than to radon), but not of other childhood cancers.

2 MATERIALS AND METHODS

2.1 Study population - cases and controls

Cases and controls are from the National Registry of Childhood Tumours (NRCT) maintained by the Childhood Cancer Research Group (CCRG) (Stiller 2007). This is a population-based registry of cancers incident in Great Britain and diagnosed before the fifteenth birthday. Further details of the NRCT are given in Appendix B. Controls matched on sex and date of birth to within six months have already been selected from the same birth register as the case for reasons unconnected with the present study. Initially one control per case was selected, but from 2000, the NRCT selected two controls per case.

At the time when the database used in this study was set up, 2006 was the latest year for which cancer registrations were essentially complete. Residential address information becomes less certain for earlier years of birth (see below), and for the purposes of this study cases were therefore defined as children born and diagnosed with cancer in Great Britain between 1980 and 2006, together with the NRCT controls for these cases. "Childhood cancer" was taken to include all diagnoses in the range ICCC3 from 11 to 122 (Steliarova-Foucher *et al.* 2005). This covers all malignant neoplasms and also brain tumours the behaviour of which is benign, malignant or uncertain. The NRCT obtains birth certificates for cases and controls. These contain a variety of information including maternal residential address at the time of the birth (for brevity "address at birth") and, in most cases, father's occupation. Records were excluded if the mother was normally resident overseas, diagnosis was made overseas or if address at birth was missing. Records were also excluded if the address was insufficiently precise. Details are given in the Results section.

Estimates of the radiation exposure of cases and controls depend on knowledge of where they lived. Addresses at birth are known for both cases and controls. Addresses at diagnosis are also known for cases, but not the equivalent addresses for controls; for consistency with controls, only address at birth is used in the analysis. In most instances an "Addresspoint" grid reference was obtained for the home address at birth of cases and controls. These are notionally accurate to 0.1m. In a minority of study subjects a grid reference was available only for the postcode within which the address fell. This might happen if, for example, the house in question no longer existed. A postcode typically covers a group of about 15 dwellings. In urban areas these are close together, but rural postcodes may cover larger areas.

Data capture for Addresspoint began in 1991 and so will not include any dwellings demolished prior to that year. The Addresspointing of the NRCT data was largely undertaken retrospectively in 2010. The proportion of untraceable addresses increases for cases and controls registered further back in time, and hence it was decided to limit the analysis to cases and controls born from 1980 onwards.

Investigations were carried out to cast light on the significance of possible movement of cases between the times of birth and diagnosis. Where the two addresses differ an analysis based on the location of postcode centroids was carried out to see how far

apart they were. Further, since the proportions of children who had moved will increase with the time between birth and diagnosis an investigation was carried out to determine the proportion of diagnosis addresses which fell within the same County District as the birth address by age at diagnosis. We also investigated the proportion of controls whose mother was resident in the same County District as that of the matched case at the time of the births in question.

2.2 Estimates of socioeconomic status (SES)

2.2.1 "Carstairs" area-based SES measure, based on census data

The Carstairs index of deprivation is a small area based measure of socio-economic circumstances (Carstairs and Morris 1991). The main source of data about the socio-economic characteristics of each area is the census which records information about the social and economic profile of the population living in each area, usually at 10-year intervals. The Carstairs index is based on 4 variables from the census:

male unemployment rates;

the proportion of households in which the head of the household is in social class 4 or 5;

non-car ownership; and

overcrowding in private households.

These four variables are measured against the national average and re-scaled so that they have the same degree of variation across the country. The resulting transformed variables are given equal weight and combined to form an overall index of deprivation. These have been calculated for census wards (these wards are of variable geographical size and population with a mean of about 5000 people of all ages) based on the data of the 1991 census. This census was chosen as representing roughly the middle of the range of birth years.

These data are complete for all cases and controls included in this study.

2.2.2 Estimate of the SES for the household based upon the occupational social class of the father.

The Carstairs Index of social deprivation provides an assessment of the socio-economic status of the general area (in this instance, census ward) in which the child lived at the time of birth. There can obviously be variation in the personal circumstances of individual households within the ward. Another way of trying to assess the SES of an individual household is to look at the occupations of the people within the household.

It is possible to make an assessment of the social class of the case or control child by looking at the occupation of the father, which is normally stated on the birth certificate. The occupation of the mother is also increasingly given in more recent years but for the purposes of this study which includes births from 1980, only the father's occupation is generally available. The occupational description was coded according to the 1980

classification of occupations (Office of Population Censuses & Surveys 1980) of the Office of Population Censuses and Surveys, OPCS (which became the Office for National Statistics, ONS). It was then possible to allocate the derived occupation code to a social class category, again using a conversion list produced by OPCS (ONS Classification and Harmonisation Unit 1985). In addition, members of UK armed forces (occupational code 135) were coded to social class 2 if it was known that they were officers and to social class 3N if it was known that they were other ranks.

This social class classification takes values in the range; 1, 2, 3 non-manual, 3 manual, 4, or 5. Social class 1 is the most skilled (i.e. likely to be the most affluent) and social class 5 the least skilled (likely to be the least affluent). Deriving social class based solely upon a self-reported occupation is somewhat limited and the occupation is missing for a significant proportion of study participants. The description given may be vague, and without further information such as employment status and professional qualifications it can often only be an indication of likely social class. For example occupation classification 076 (Engineers not elsewhere classified) is assigned to social class 1. This would be appropriate for graduate engineers, but in conventional English usage “engineer” describes a wide range of occupations requiring differing skills and experience. However, there should be no bias in accuracy between cases and controls and adopting the OPCS standard allows for comparison with national figures.

2.3 Estimates of indoor gamma ray dose rates

Data on indoor gamma ray absorbed dose rates come from a National Survey of natural radiation which was undertaken in the 1980s by Wrixon *et al* (Wrixon *et al* 1998). Indoor gamma ray dose rates were estimated using thermoluminescent dosemeters (TLDs) in two rooms of 2333 selected houses over a six-month period. These TLDs also measured the directly ionising component of doses from cosmic rays. Since both cosmic rays and terrestrial gamma rays give doses which are effectively uniform across the body it is more satisfactory to consider gamma and directly ionising cosmic ray doses together rather than to attempt to separate the two components. For brevity we will describe these combined doses as “gamma ray dose”. Further discussion of the gamma ray dose estimates can be found in Kendall et al (Kendall *et al* 2006). In particular, Kendall et al re-analysed the data of the National Survey to give mean gamma ray dose rates in English County Districts and in comparable administrative areas elsewhere in Great Britain. There are 459 such units in GB with a mean population of about 120,000 in 1991 and it is these data which are used in the present analysis.

The data of the National Survey are now over 20 years old. However, there is no reason to believe that gamma ray levels will have changed significantly with time. An independent source of information on natural radiation exposures was the UK Childhood Cancer Study (UKCCS). This was a large case-control study of childhood cancer undertaken in the United Kingdom in the early to mid 1990s. As part of this study, measurements of gamma ray dose rates were made in the dwellings in which 5086 control children had lived (UK Childhood Cancer Study Investigators 2002b) (UKCCS Investigators 2002). The data reported by the UKCCS appear consistent with

the results of the National Survey by Wrixon et al (Kendall *et al* 2006). The UKCCS investigators presented data for nine Regions, but not for smaller geographical units that could be compared with the data of the National Survey.

The main analysis in this report uses an exposure integrated from birth to diagnosis (which is roughly equivalent to the period from conception to nine months before diagnosis). This is the same period as that used Raaschou-Neilsen et al (2008). However, we also explore the effect of analysing in terms of the accumulated exposure or dose from conception to diagnosis with latent periods of 0, 1 and 2 years. Results for the 1 year latency will, of course be similar to those for 9 months latency but the former may be more convenient for comparison with some other published data.

The main analyses use gamma ray doses integrated over the exposure period in question. These were expressed in mGy. For analyses in terms of dose rate, units of μGy per day were used. The choice of units for gamma ray dose rates does not affect the chance that results will achieve statistical significance, but it can give results in a more convenient numerical range.

When the effects of gamma rays and of radon are being examined together both must be expressed in terms of the equivalent dose (or a similar weighted absorbed dose) to the relevant organ or tissue for the endpoint being considered. In this work we have undertaken analyses of leukaemias in terms of the red bone marrow dose from radon, from gamma rays and from both sources combined. The gamma ray quantity measured in the National Survey was absorbed dose to air in air. The RBM dose from gamma rays varies somewhat with age (Kendall *et al* 2006), and for the present work a conversion factor has been estimated based on the total dose up to the fifteenth birthday, taking account of indoor occupancy. Measured doses in mGy were converted to approximate equivalent dose to the red bone marrow by multiplying by a factor of 0.79.

2.4 Estimates of radon exposures of cases and controls

Two sources of estimates of radon concentrations in the homes of study participants were available to the study. The first was averages in County Districts, based on the results of the National Survey (Wrixon *et al* 1998). These are simply the radon analogues of the gamma ray estimates described above, though only 2093 radon estimates contributed to these County District means. The second source of estimates of the radon concentrations in the homes of cases and of controls was a predictive radon map based on both the results of measurements of radon concentrations in homes and on information about the boundaries between different geological units. This was the result of collaborative work between the Health Protection Agency (HPA) and the British Geological Survey (Appleton and Miles 2010; Miles and Appleton 2005; Miles *et al.* 2007). It offers much more detailed radon predictions than the County District means.

The HPA/BGS mapping was based on over 400,000 radon measurements in homes and on the boundaries of both bedrock and superficial geology. Geological boundaries provide a more logical means of grouping radon results than any administrative

boundaries, since most indoor radon is derived from the ground. Other geological indicators, such as the nature of the underlying rock or the results of measurements of radon in soil gas, were not used. Gunby et al (1993) (Gunby *et al.* 1993) showed that the distribution of radon concentrations in UK homes was lognormal after subtraction of the mean outdoor radon concentration. For this reason, the radon mapping method was based on geometric means and geometric standard deviations of the results of measurements after subtraction of outdoor radon.

Maps were constructed by grouping measurement results according to the combination of bedrock and superficial geology that they lie on, and then mapping variations in radon results within each geological combination by 1 km squares of the UK National Grid. The predicted radon potential for any location on the map is based on the radon measurement results from the thirty nearest homes on the same geological combination as the target location. The mapping used about 400 combinations of underlying and superficial geology and produced a map of about one and a half million polygons combining geology and grid square.

Estimates of geometric standard deviation based on thirty results were corrected using Bayesian methods, taking account of a knowledge of the underlying distribution of geometric standard deviations (Miles and Appleton 2005). The measured geometric standard deviations are also affected by uncertainties in the estimates of long-term mean concentrations in homes caused by year-to-year variations in indoor concentrations. Account was taken of this effect (Miles and Appleton 2005).

About 20% of the homes in the UK are located on geological combinations for which the indoor radon data are too sparse to allow the method described above to be applied. In these cases more approximate methods are used (Miles and Appleton 2005). Areas of low measurement density will generally be those where radon levels are low or where few people live.

The radon map provides estimated percentages of homes above the UK Action Level for radon (200 Bq/m3). For this study, estimates of radon concentrations in homes are required. These were calculated from the geometric mean radon concentrations and geometric standard deviations underlying the published map.

Estimates of radon exposures (Bq per m^3) in the homes of all individuals in the study are made using the best available grid reference (that based on Addresspoint or, failing that, Postcode) for the place of birth of the case or control. There are thus four types of radon estimate: those based on:

Gridsquare mapping and Addresspoint

Non-gridsq mapping and Addresspoint

Gridsquare mapping and Codepoint

Non-gridsq mapping and Codepoint

The first of these “GridSquare/AP” estimates is more likely to be accurate than the other categories. However, all four provide estimates of the likely average concentration in the area in question rather than an estimate specifically for the dwelling in question. Significant uncertainties attach to all these estimates. Where a GridSquare/AP estimate is not available, but there were estimates based on both Non-gridsq mapping and Addresspoint and on Gridsquare mapping and Codepoint the former was preferred. This was because in a few cases it is possible that the more precise geographical location will indicate that the house lies on a different geology than that suggested by the Postcode location. This is more likely to affect the estimate of the radon concentration significantly than more sophisticated mapping

Appendix C discusses the HPA/BGS radon estimates in more detail.

The radon concentration in a dwelling is proportional to the dose rate to which those living there are exposed. Another measure of radiation risk is the cumulative exposure. This was estimated as the product of the radon concentration in the place of birth and the length of time before cancer was diagnosed in the case. For consistency with other published work this was expressed as kBq m^{-3} years.

Estimates of equivalent dose to the red bone marrow from radon require detailed modelling of the distribution and retention of both radon gas and of the radon decay products within the body (Kendall *et al* 2009). Both the volume of air inhaled (and thus the amount of radon taken in) and the dose per unit intake are age dependent. However, to good approximation these factors cancel and the annual red bone marrow dose can be taken as independent of age for the period from birth to the fifteenth birthday. At the UK national average radon concentration of about 22 Bq m^{-3} pa the annual RBM dose from radon and decay products has been estimated to be 80 micro Sv (Kendall *et al* 2009). This implies that the time integrated concentrations used in the present analysis (kBq m^{-3} – years) are to be multiplied by 3.4 to give mSv RBM equivalent dose.

2.5 Statistical methods

The analysis used conditional logistic regression implemented in STATA (StataCorp 2009) and matched case-control sets (one or two controls per case). In the main analysis time integrated radon concentrations and gamma ray doses are treated as a continuous variable. Where we have two controls per case both are included in the analysis. As described below the main analysis considers case-control sets with all grades of radon estimation. A subsidiary analysis is for case-control sets where all records have a radon potential based on the addresspoint location of the address and detailed radon mapping.

A log-linear logistic model (Breslow and Day 1980) is fitted via maximum likelihood (McCullagh and Nelder 1989), in which $OR = \exp[\alpha_1 D]$ (D = cumulative dose) or equivalently, $P[\text{case} \mid \text{dose } D] = \dfrac{\exp[\alpha_0 + \alpha_1 D]}{1 + \exp[\alpha_0 + \alpha_1 D]}$.

The odds ratio (OR) is here equivalent to the relative risk. Confidence intervals (CI) are Wald-based, calculated using the Fisher information (Cox and Hinkley 1974). Tests for heterogeneity were carried out using the Mantel–Haenszel command for gamma ray and for radon exposures separately.

The p-values presented (e.g., for trend and heterogeneity) are for two-sided tests.

Further details of the statistical methodology are in Appendix D.

2.6 Choice of principal analysis

As noted above, a number of dosimetric quantities are available for the analysis, two alternative measures of SES and a large number of disease groupings. The analysis to which most weight should be given was decided before any results from the study had been calculated. Subsidiary analyses would be carried out to explore variants on the main analysis. It was decided that the main analysis would adopt the following:

1. SES variable

   Quintile of the distribution of the Carstairs score would be included in the analysis. The Carstairs score is complete and objective; father's social class is individual based but is incomplete and depends on self-reported occupation.

2. Time integrated radiation quantities versus dose rate quantities

   The accepted models for radiation risks use accumulated dose rather than instantaneous dose rate as the relevant quantity. It was therefore decided that the principal analysis would use radon concentrations and gamma ray dose rates integrated over an "at risk" period. There is evidence that *in utero* doses confer an excess risk of childhood leukaemia and probably also for other childhood cancers (Bithell and Stewart 1975; Wakeford and Little 2003) (Bithell and Stewart, 1975; Wakeford and Little 2003). It is clear that a cancer will have completed the various steps in development before it is diagnosed, and that some latent period should therefore be allowed to take account of exposures when the cancer has developed but has not yet been diagnosed. For childhood cancers this period may be short, but it is likely to differ for different cancer types and for diagnoses at different ages. It was decided to analyse the data in terms of the dose accumulated in the period between birth to the time of diagnosis; this is, roughly equivalent (for constant dose rate) to the period from conception to nine months before diagnosis. Subsidiary analyses would explore different assumptions about the appropriate latent period.

   In principle increased power would be obtained by analysing in terms of combined radon and gamma doses to the relevant organ or tissue for each cancer type. However, of the most important disease groupings, methods for organ dose estimation were available only for leukaemia, and even here there were considerable uncertainties regarding the radon contribution. The main analysis would therefore not consider combined radon and gamma organ doses.

3. The main analysis would use the HPA/BGS radon mapping because of its greater spatial resolution. It would include all radon measurements rather than just those based on AddressPoint location and the most detailed level of grid square modelling. No matter how accurate the estimation of mean radon levels in an area there will be large differences between individual houses. Moreover, where a low measurement density precludes the most detailed level of grid square mapping the radon levels will often be low.

4. Diagnostic categories

   Before the first analyses were undertaken it was decided that the main analyses would consider three endpoints:

Lymphoid Leukaemia	(ICCC3 11)
All leukaemias	(ICCC3 11-15)
All Cancers	(ICCC3 11-122)

   Childhood leukaemia is strongly linked with radiation exposure. Lymphoid leukaemia is the largest category of childhood leukaemia. All childhood cancers is also clearly a category of interest.

3 RESULTS

3.1 Study population - cases and controls

The study population was defined as all cases of childhood cancer born and diagnosed in Great Britain between 1980 and 2006 together with the NRCT controls for these cases. Records were excluded if the mother was normally resident overseas (23 cases and their matched controls) or if address at birth was missing (2 cases and their matched controls). Records were also excluded if the address was not known with sufficient precision. Records were included if the street of residence was traced in the Postcode Address File (PAF) even if the exact house number was not; they were excluded if there was uncertain identification of street or if only the town was specified. The study population is described in Table 3.1; 407 cases and 468 controls were excluded because of imprecision in their addresses.

The analysis file contained 64240 records, 27447 cases and 36793 controls. These comprised 9346 sets of a case and two controls and 18101 sets of a case and one control.

As described in Section 2, addresses were assigned grid references using the addresspoint system or, if this was not possible, the less precise codepoint (Martin and Higgs 1997). Table 3.1 shows that addresspoint grid references were available for over 96% of records overall with very similar proportions for cases and controls. For those cases and controls for whom an addresspoint grid reference for the mother's residence

at the time of the birth of the child was available, the mean separation of the postcode centroid and the addresspoint grid reference was 90m for cases and 91m for controls.

Information on migration of cases (i.e. movement from the birth address by the time of diagnosis) is in tables 3.2 and 3.3. The total number of cases in these tables is slightly smaller than the overall total because in very few cases (38) the address at diagnosis was known imprecisely. Table 3.2 gives a breakdown - based on the location of the appropriate postcode centroids - of the distance between the addresses at birth and at diagnosis for cases. Postcodes were chosen because they are available for all cases and controls (Table 3.1). Table 3.2 shows that (for all childhood cancers together) address at diagnosis is the same as address at birth for about half the cases included in the analysis and a further 20% had moved less than 2 km, while 80% had moved less than 5 km. The mean distance between the address at birth and that at diagnosis was about 30 km for cases who had moved and about 16 km for all cases. There are some differences in these figures between different diagnostic groupings, reflecting the differing distributions of age at diagnosis. The figures for leukaemia are similar to those for all childhood cancers taken together.

Table 3.3 gives data broken down by age at diagnosis of the number of cases which were still resident in the County District of birth at the time of diagnosis. For all childhood cancers taken together 96% of those diagnosed in the first year of life were still in the County District in which they were born. This figure dropped to 75% for those diagnosed at age 14 years. For all ages the figure was 83%. As with the distance between address at birth and at diagnosis, the figures for leukaemia are similar to those for all childhood cancers taken together. Slightly more children who developed lymphoma had moved from the County District of birth by the time of diagnosis, reflecting the different distribution of age at diagnosis.

As described above there is a degree of geographical matching between the place of birth of the cases and their matched controls. This is quantified in Table 3.4. The mean separation between place of birth of controls and their matched case is about 11 km. This figure does not vary significantly with diagnostic grouping. About half of the controls were born more than 7 km from the matched case. The approximate matching of cases and controls on place of birth could result in them having the same estimated radiation exposure. This is explored in later sections.

Table 3.5 gives the breakdown of the cases by age at diagnosis, sex and diagnostic grouping. About 12% of all tumours arose in children before their first birthday, 43% in those aged 1-4, 25% in those aged 5-9 and 20% in those aged 10-14 years. There were rather more cases of childhood cancer in boys (about 55% of the total) than in girls. About one third of cancers are leukaemias, about a quarter tumours of brain and CNS and rather more than a third in the “other malignant tumours” category.

When comparisons are made between cases and their matched controls the mean absolute difference (i.e. regardless of whether positive or negative) between the dates of birth is 13.5 days, with 95% being within five weeks. However, controls were born both before and after their matching case and the mean difference is less than one day. Ages at diagnosis are thus 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. This is due to the influence of the second controls (Appendix E) 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.

More detail about the Study Population is in Appendix E.

3.2 Estimates of socioeconomic status (SES)

3.2.1 "Carstairs" area SES based on census data

The quintile category of the Carstairs index of deprivation is available for all cases and controls included in this study. Table 3.6 gives a two-way table of Carstairs quintile against social class based on father's occupation (see next section) and further details are in Appendix E. The proportions of records in each quintile are very similar for cases and controls and increase steadily from about 12% in quintile 1 to 34% in quintile 5. Note that the quintiles are of census wards which are of different sizes. It would not therefore be expected that 20% of all cases and controls would fall in each quintile.

3.2.2 Estimate of the SES for the household based upon the social class of the father

This measure of social class was available for a majority (about 90%) of cases and controls included in this study (Table 3.6). It is based on the father's occupation as given on the birth certificate and limited information is available on employment status and qualifications. Father's social class was not available for 6646 records. In almost 80% of these cases the father's occupation had not been specified on the birth certificate. In the remaining cases an occupation had been specified, but this could not be interpreted in terms of social class (e.g. "Full time student"). Data in Appendix E shows that the overall distribution of social class of the fathers is very similar for cases and for controls.

The largest group of study participants (32% of those for whom the social class was known) had fathers in social class 3M with about 24% in social class 2, 17% in social class 4, 13% in social class 3N, 8% in social class 1 and 6% in social class 5. However, study participants for whom no social class could be assigned tended to fall in lower Carstairs Quintiles than did study participants as a whole.

When compared with published ONS data for the 0-15 age group (Office for National Statistics 2011), the distribution of Table 3-6 shows fewer people in social class 2 (24% vs 31%) with the deficit spread over lower social classes. The social class data for this study are based on father's occupation as given on the birth certificate. The ONS data are based on a 10% sample of the census. This will usually have been later than the time of birth of the children. It is possible that the family might have become more affluent, with the parents moving to an occupation associated with a higher social class, in the intervening time.

However, the father's social class can be used in the analysis only for case-control sets where both case and control(s) have been assigned a value. While father's occupation

can be used to assign a social class for 24921 case records and for 32673 controls, the numbers of these which are in sets for which case and control(s) both have such a social class measure are only 23441 and 29946 respectively (Appendix E). In some cases, one control has been dropped from a case-control triplet set to leave a doublet set which can be included in this analysis. Father's social class was thus available for about 91% of records, but for only 85% of records in case-control sets for which this variable was complete. Rather more cases (85%) than controls (81%) survived in this analysis. This is because the lack of social class for a case inevitably excludes its control(s), while the lack of social class for only one control in a case-control triplet set leaves a doublet set which can go forward to the analysis.

The expected correlation between the two measures of SES can be discerned. The correlation coefficient between Carstairs (expressed as Quintiles) and occupational social class (6 ONS categories) is 0.28 ($p<0.001$) based on 57594 individuals (i.e. cases and controls together). For cases the value is 0.29 ($p<0.001$) based on 24921 individuals and for controls the value is 0.27 ($p<0.001$) based on 32673 individuals. These correlations are highly statistically significant because of the large numbers involved; they are however, not particularly strong. It should be borne in mind that one measure is area-based whereas the other is individual-based.

3.3 Estimates of indoor gamma ray dose rates

Estimates of indoor gamma ray dose rates are available for all cases and controls. Parameters describing the distributions of absorbed dose rates (nGy per hour) for cases and controls are given in Table 3.7. Mean values and standard deviations are very similar between cases (94.9 ± 15.7 nGy h^{-1}) and controls (94.7 ± 15.6 nGy h^{-1}). The distribution of gamma ray dose rates is approximately normal.

Since controls are selected with a degree of geographical matching with the case, an important question is the number of cases and controls which have the same estimated gamma ray dose rate. The number of cases with a different gamma ray dose rate from their control(s) was 14308 (52% of all cases) and the number of controls with a different gamma ray dose rate from their case was 17532 (48% of all controls). Cases and controls which share the same estimate of gamma ray dose rate are likely to be less informative than those with different estimates because their time integrated doses will differ only because of different periods at risk.

While gamma ray dose rate is the primary measured quantity, for the analysis we also need to consider two other quantities: time integrated dose to diagnosis, or pseudo diagnosis for controls, and estimated cumulative equivalent dose to the red bone marrow (the latter being relevant only for investigations of leukaemia). The time integrated dose is estimated simply as the product of the gamma ray dose rate and the age at diagnosis. These time integrated exposures to the time of diagnosis will, of course, be greatly affected by the age at diagnosis. Gamma ray doses integrated to the time of diagnosis were similar between cases and controls (4.65±3.66 vs 4.85±3.74 mGy respectively). Distributions of gamma-ray doses by attained age for cases and

controls for the disease groupings all leukaemias and all other cancers are given in Appendix E.

The correlation between radon concentration and gamma ray dose rate is 0.09 ($p<0.001$). For cases the value is 0.10 ($p<0.001$) and for controls the value is 0.09 ($p<0.001$). Correlations for time integrated quantities would be very similar. This correlation is highly statistically significant because of the large numbers involved. However, it is not strong.

3.4 Estimates of radon concentrations in the homes of cases and controls

Estimates of radon concentration in the place of birth are available for all cases and controls. These radon estimates fall into four classes, as described in Section 2; the breakdown of the measurements into these four classes is detailed in Appendix E. A large majority (almost 90%) are based on the most detailed radon mapping based on grid square and geology and on location specified by Addresspoint ("GridSquare/AP" estimates). In some cases (8%) the Addresspoint location was known but more approximate radon mapping had to be used. Where the Addresspoint was not known (about 4% of all cases and controls) the radon estimate was usually based on the most detailed radon mapping for the location of the postcode (3%) but sometimes on approximate radon mapping for the location of the postcode (1%). However, no matter how accurate the estimate of the mean and standard deviation for an area, there will be considerable variation in the radon concentrations in different houses. It was therefore decided before the analyses were undertaken that the main analysis would use all radon estimates.

The main analysis of associations between radiation exposure and childhood cancer uses all types of radon estimate on the same footing. A subsidiary analysis is restricted to those case/control sets where all members had GridSquare/AP radon estimates. A total of 24664 cases and 33068 control records had such radon estimates, 90% of the total in both cases. However, when attention is restricted to case/control sets all of whose members have GridSquare/AP estimates, 23021 cases and 30270 controls (84% and 82% of the totals) survive.

Since controls are selected with a degree of geographical matching with the case, an important question is the number of controls which have the same estimated radon concentration as the case. The number of cases with same estimated radon concentration as their controls is 890, about 3% of the total number of 27447 cases. The number of controls with same estimated radon concentration as the case is 1518, about 4% of the total number of 36793 controls.

Table 3.8 summarises parameters describing the distributions of radon concentrations for all records, for records having GridSquare/AP estimates, for cases and for controls. Mean estimates of radon concentration and standard deviations are similar for all radon estimates and for those based on GridSquare/AP estimates (21.3 ±23.0 and 21.7±24.2 Bq m^{-3} respectively) and for cases and controls (21.3 ±23.7 and 21.3±22.6 Bq m^{-3} respectively).

The distributions of radon measurements are skew and more closely approximate a log-normal rather than a normal distribution. The observation of an approximately normal distribution for gamma ray dose rates and an approximately log-normal distribution for radon concentrations is expected (Wrixon et al, 1988).

The time integrated radon exposures proved to be very similar between cases and controls, 0.119±0.19 and 0.124±0.19 kBq m^{-3} years respectively. Distributions of cumulative radon exposures by attained age for cases and controls for the disease groupings all leukaemias and all other cancers are given in Appendix E. Appendix E also gives distributions of cumulative gamma ray and radon exposures by Carstairs quintile for cases and controls. As expected, radon exposures vary with SES while gamma ray exposures do not. No differences between cases and controls in this respect are apparent.

The mean RBM doses from birth to the time of diagnosis were 0.50 and 0.53 mSv for cases and controls respectively. These are, of course, the time integrated exposures scaled by the appropriate factor.

3.5 Trend analyses

Table 3.9 gives the results for the main trend analysis using radon and gamma ray exposures integrated to the time of diagnosis and using Carstairs quintiles as a measure of SES. Before the analyses were undertaken it was decided that this would consider three endpoints: lymphoid leukaemia, all leukaemias and all cancers. These would be analysed in terms of time integrated radiation variables (i.e. radon concentration and gamma ray dose rate multiplied by age at diagnosis) with Carstairs Quintile as an SES variable. For compactness Table 3.9 and later tables include end points other than the three selected beforehand as of greatest significance.

In the main analysis including both time-integrated radon exposure and time integrated gamma ray exposure, elevated relative risks (RR) were found for gamma ray exposures for all three specified end points: lymphoid leukaemia, all leukaemias and all cancers. All three of these RRs reached the conventional level of statistical significance (p=0.01, p=0.01 and p=0.04 respectively; all p values 2-sided). Lymphoid leukaemia is, of course the largest component of the all leukaemias group and leukaemia makes up about one-third of all childhood cancers. The findings are thus not independent. Other disease groupings in Table 3.9, lymphoid leukaemia with non-Hodgkin lymphoma and all leukaemia with non-Hodgkin lymphoma also reach statistical significance, but again these are driven by the data for lymphoid leukaemia. The radon RRs are elevated for several disease groupings but none is close to statistical significance.

Table 3.9 also gives the RR per Carstairs quintile. This shows the expected higher risk of leukaemia in more affluent groups.

Table 3.10 gives results for calculations in which an alternative allowance for socio-economic status was made. In Table 3.9, Carstairs Quintile was included in the analysis. Table 3.10 gives results in which the radiation variables were included together with, as SES parameter, father's social class based on occupation as recorded

on the birth certificate. In this analysis the general pattern of results was similar to the main analysis but no RR was significantly raised at the two-sided 0.05 level. This analysis includes rather fewer cases and controls.

Table 3.11 presents results for an analysis similar to the main analysis (Table 3.9) but using Carstairs deprivation scores rather than quintiles of the distribution of these scores. The gamma ray results are almost unaffected. RRs for radon are perhaps a little higher in the main analysis, but any differences are small.

Table 3.12 gives results for calculations in which the radiation variables were considered without allowance for any SES parameter. The results were broadly similar to those for the main analysis but the elevated RRs were generally somewhat less significant; that for total childhood cancer in the gamma ray analysis no longer reached the conventional 5% level for statistical significance. Some of the radon RRs were somewhat closer to statistical significance.

Table 3.13 gives results for the time integrated radiation variables separately (ie for gamma-rays without radon and vice-versa) with allowance for SES. In these analyses the results for both gamma rays and for radon were broadly similar to those in the main analysis, which is unsurprising given the weak correlation between the two exposures.

Table 3.14 gives the results of an analysis similar to those of Table 3.9, but was restricted to case/control sets with GridSq/AP radon estimates, ie the most precise radon estimates. The results were broadly similar to those of Table 3.9, but the RRs were less significant, that for total childhood cancer having a p value of 0.22 (2-sided). This analysis included fewer case/control sets than the main analysis of Table 3.9.

Table 3.15 presents results for an analysis similar to the main analysis (Table 3.9) but using an alternative estimate of radon exposure - the mean for the County District in which the mother was resident at the time of the birth of the study participant. These County District means were estimated from the results of the National Survey (Kendall *et al* 2006; Wrixon *et al* 1998). They are the radon analogue of the gamma ray estimates used throughout this study. Using these alternative radon estimates the RRs for gammas are essentially unaffected. Those for radon are generally closer to one than those of the main analysis.

Table 3.16 gives the results for an analysis similar to the main analysis of Table 3.9 but taking dose or exposure rates as a measure of radiation exposure rather than exposures integrated to the time of diagnosis. Most of the RRs were above unity but none reached statistical significance under a 2-sided test.

Analyses were also carried out using estimates of equivalent dose to the red bone marrow integrated up to the time of diagnosis. These doses are proportional to the time integrated exposures and the analyses generally add little to those of Table 3.9. However, it is now possible to combine the estimated RBM equivalent doses from radon and gamma rays to give an overall estimate of radiation dose to the time of diagnosis. The results of this analysis are given in Table 3.17. The results for leukaemia are similar to the gamma ray results in Table 3.9. Some of the (2-sided) significance levels that were close to 0.01 have moved a little higher or lower, but we do not regard these changes as important. Note that while equivalent dose to the RBM is plausibly a

measure of the likelihood of induction of leukaemia it is not generally appropriate for analyses of other disease groupings.

Table 3.18 gives RRs for males and females separately using the same model as Table 3.9. The general patterns of results are similar to those of Table 3.9. There are fewer female than male cases and the significance levels for the RRs for females are generally greater than those for males. The difference in radon RR for "other leukaemia" between males and females is statistically significant (Table 3.24); however, this may well be a chance result.

Tables 3.19 and 3.20 examine the RRs for different categories of age at diagnosis, ages less than one year, 1-4, 5-9 and 10-14 years. For radon, nominally statistically significant RRs are found for some categories of leukaemia and lymphoma, although given the number of significance tests are being carried out it is unclear how much importance should be attached to these findings. For radon, differences in radon RR across the four age groups are statistically significant for two disease groupings (Non-Hodgkin lymphoma and total lymphoma), see Table 3.24. These may well be chance results.

Table 3.21 presents a more detailed breakdown by single year of age at diagnosis for lymphoid leukaemia. No particular pattern is suggested by the radon results. The gamma ray results should not be over-interpreted since some of the points rest on only a couple of hundred cases. However, there is a suggestion of a peak in the RRs roughly between ages 5 and 12 years with a peak at 9 years of age. There is little evidence for heterogeneity between the RR for single years of age at diagnosis (Table 3.24); we do not attach any significance to the heterogeneity in gamma ray RR for the disease grouping "other malignant tumours".

Tables 3.22 and 3.23 explore the consequences of different assumptions about latent period. As noted above the main analyses of Table 3.9 consider dose incurred over the period between birth and diagnosis of the case, which is roughly equivalent to the period from conception to nine months before diagnosis. These two tables also consider latent periods of zero, 12 and 24 months. Results with latent periods of 9 and 12 months are almost identical and results for all four latent periods are very similar. There is perhaps a slight tendency for results to be more significant for longer latent periods, but generally RRs hardly change.

4 DISCUSSION

4.1 Introduction

It is established beyond reasonable doubt that high doses of ionizing radiation received after birth will increase the risk of childhood leukaemia (UNSCEAR 2008), and there is also evidence that low doses received *in utero* during medical radiography also increase this risk (Doll and Wakeford 1997). For childhood cancers other than leukaemia the evidence for postnatal exposure to radiation increasing the risk is more limited (with the exception of thyroid cancer, which is rare in childhood); but there is

evidence that antenatal exposure raises the risk of the typical cancers of childhood to about the same extent as for childhood leukaemia (see section 1.3), although this remains controversial (Boice and Miller 1999).

Recent calculations (Little *et al* 2009; Wakeford *et al* 2009) have applied the latest leukaemia risk models derived from the experience of the Japanese atomic bomb survivors exposed after birth, to the RBM doses received from natural background radiation in Great Britain, and obtained estimates of the proportion of childhood leukaemia incidence that may be attributable to such exposure. The studies concluded that this attributable proportion is likely to be in the range 15-20%, this range reflecting the possible variation in the effectiveness of alpha particles in inducing childhood leukaemia. However, the authors pointed out that there are other substantial uncertainties in estimating this attributable proportion, and that some of these are less easy to quantify. These include the way in which risks calculated for a Japanese population in the 1950s should be transferred to the current UK population, and uncertainties in the risk models themselves.

Little et al (Little *et al* 2010) examined the variation of the RBM dose received from external gamma radiation and radon in Great Britain and how this affected the size of epidemiological study of childhood leukaemia required to have a reasonable statistical power to detect the effect of these sources of natural background radiation upon the risk of childhood leukaemia. These power calculations were based upon the predictions of leukaemia risk models applied to annual RBM doses for the population of Great Britain. The findings of Little et al (Little *et al* 2010) suggest that previous studies that have attempted to detect an association between natural sources of radiation and childhood leukaemia have been too small to have a realistic chance of detecting the level of association predicted by recent risk models and RBM dose estimates. A number of these previous epidemiological studies also suffer from other problems, such as participation bias and uncontrolled confounding.

The nationwide case-control study described here is, based upon power calculations like those of Little et al (Little *et al* 2010), sufficiently large to have a reasonable chance of detecting the predicted effect of the RBM dose received from external gamma radiation from natural sources upon the risk of childhood leukaemia (although much less so for the RBM doses from radon), and the statistical associations must be viewed in this context. Further, potential common sources of bias are absent from the study – for example, it is free of participation bias that can seriously affect interview-based case-control studies, and the radiation exposures and SES classification of cases and controls are made on the same footing, so that information bias is avoided. However, the record based study design, without individual approaches to cases and controls, which is responsible for the formidable advantages of this type of study, carry inescapable disadvantages. It is necessary to rely on estimates of radiation exposures for study participants from previous areal surveys. These are likely to be less accurate than individual measurements on the homes of those concerned. Equally, information on possible confounders, in particular socio-economic status will not be based on interview.

Following the methodology of Little et al (Little *et al* 2010), a case-control study having the number of leukaemia cases included in the present study and one or two controls

per case, with a geographical distribution of gamma ray doses as County District averages, has a power to detect the predicted level of association between gamma ray dose and leukaemia significant at the one-sided 0.05 level of about 68%. However, in the present study approaching half the cases are assigned the same gamma ray absorbed dose rate as their matched control(s) and these cases/controls contribute power to the gamma ray analysis only to the extent that the at risk period differs between cases and controls. The estimated power of this study with respect to the gamma ray exposure component is thus hard to assess precisely, but in round terms is likely to be about 50%, which is still a reasonable power to detect the level of predicted effect. Given the higher areal resolution of radon exposure estimates, this problem of dose-rates common to cases and matched controls is effectively absent for the radon component of the study; but the smaller RBM doses from radon mean that the power of the study to detect the predicted effect is low.

A power calculation can provide some insight into the possibility that the results obtained are subject to conditioning bias. Conditioning bias is simply the result of conditioning on a smaller subset of the probability space, in this case the subset corresponding to the samples in which the trend statistic is significantly greater than 0. As demonstrated by Land (Land 1980), a statistically significant result from a severely underpowered study is more likely to be subject to this kind of bias. As we show in Appendix F, conditional on there being a statistically significant trend with dose (as is the case here for gamma radiation), this will result in the trend estimate being biased upwards (by about 0.8 of a standard deviation). However, as we discuss there, and as pointed out by Land (Land 1980), the critical point is not the central estimate but the coverage probability, i.e. the probability that CIs contain the true value. As we show in Appendix F, in our case the 95% CI for the estimate of trend with dose has about 95% coverage, which we judge to be acceptable. As noted above conditioning bias is the result of conditioning on the subset of the probability space corresponding to the samples in which the trend statistic is significantly greater than 0. Without conditioning on this, i.e. making no assumptions about the significance or otherwise of the trend test, the estimate will be unbiased. This sort of bias is clearly distinct from various other sorts of bias that can occur in epidemiological studies (and specifically case-control studies), in particular selection bias, e.g. a tendency to recruit preferentially higher dose cases than controls; selection bias would not be expected in this study given the register-based methods that are used to select cases and controls.

In principle, it is possible that the sampling strategy used in the collection of gamma ray data might introduce bias as might measurement errors in the dosemeters themselves. These matters are considered in Appendix G. We conclude that any such biases are very small.

4.2 The socio-economic status and radiation data used in the study

4.2.1 Socio-economic status

The Carstairs score gives an estimate of the mean Socio-economic status (SES) within a census ward (Carstairs and Morris 1991). There will clearly be variation in SES

between individuals within the wards. The estimate of father's social class, based on his occupation as given on the birth record might appear to be preferable in this respect. However, it is incomplete, self-reported and relates to occupation at the time of the child's birth rather than over later periods in the child's life. The Carstairs quintile was therefore preferred in our analyses. It would be expected that the two measures of SES are correlated and this was found to be the case. The correlation was highly significant ($P<0.001$) because of the large number of participants in this study. However it was not particularly strong (correlation coefficient =0.29).

4.2.2 Gamma ray exposures

For this study estimates of mean indoor gamma ray dose rates (including the contribution from directly ionising cosmic rays) in County Districts (CDs) were used for cases and controls. County Districts contain on average about 100,000 persons (of all ages) and smaller areas would have been preferable had the measurement density allowed this. This would both improve the accuracy of estimates for cases and controls and reduce the proportion of matched case-control sets that are assigned the same estimate thereby increasing statistical power.

Both indoor gamma ray dose rates and indoor radon concentrations are affected by a number of factors (Kendall *et al* 2006). The main determinants of indoor gamma ray doses are

a the local geology, in particular the concentrations of potassium-40 and of uranium and thorium with their decay products in the locality, which affect the intensity of gamma rays outside the house,
b the shielding against this radiation provided by the fabric of the building, and
c the contribution added to the shielded indoor dose rate from radioactive decays in the building materials themselves.

In addition to the contribution to dose from gamma rays, the dose from directly ionising cosmic rays will be reduced by shielding from the material of the house. It will also be affected by latitude and altitude (Kendall *et al* 2006), but in the UK, where most of the population live close to sea level, these effects are not substantial.

Overall it is found that the house-to-house variation in dose rate is smaller for gamma rays than for radon. Gamma ray dose rates are distributed roughly normally with a standard deviation which is around 16% of the mean, while radon concentrations are distributed roughly log-normally with a (linear) standard deviation close to the mean.

For both radon and gamma rays there are factors which may make the dose rates (or radon concentration) in a house significantly different from that in the next door building. For radon the differences are the substrate to the house and the resulting radon concentration in the soil gas beneath the house, the extent to which cracks or gaps in the floor of the house permit radon ingress and the pressure difference between inside and outside which will drive the flow. For gamma rays the external dose rate from local soils can differ, but the largest potential difference between adjoining house arises from the building materials from which they are constructed. Under many circumstances these will be similar, particularly where local materials are used, but significant variations are possible.

The result of a measurement of radiation levels in the house of a study participant will differ from the mean for the local area for two reasons. Firstly, the levels in the house in question will genuinely differ from the mean for the area. However, in practical situations there will also be random measurement errors associated with any particular measurement. These random errors will affect the mean for the local area to a smaller extent than for the individual measurements. While direct measurements in the houses of study participants are to be preferred, the smaller role for measurement errors compensate to some extent if estimates for local areas are used. A further consideration, discussed below, is that use of estimated radiation levels for the local area will to some extent reduce the effect of migration: study participants who move from one address to another will retain the same estimated radiation exposure if they remain within the same local area. This effect is larger for larger areas such as the County Districts used for gamma ray estimates.

There is little difference between the gamma ray dose rates for cases and controls, although there is a tendency for cases to be a little higher at older age groups. However, the quantity of greater relevance for the tests for trend with dose is the cumulative dose from birth to diagnosis. Distributions of gamma-ray doses by attained age for cases and controls are given in Appendix E for the disease groupings all leukaemias and 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 the Methods section is required; the resulting variation in RR with cumulative dose is presented below.

4.2.3 Radon concentrations

The radon concentration values used in this study are estimates of the mean radon concentration in small areas of variable size (Miles and Appleton 2005). These areas, which comprise about one and a half million polygons combining geology and grid square, will tend to be smaller in areas of relatively high radon concentration, where many radon measurements have been made and large where radon levels are lower. However, even if the average radon concentration in an area is known exactly there will be substantial variation from one house to another. Unlike the Danish study of Raaschou-Nielsen et al, we had no information about the type of dwelling occupied by study participants (Andersen *et al* 2007; Raaschou-Nielsen *et al* 2008); this would have allowed a somewhat more refined estimate of mean predicted radon level though the effect would be small since the details of house construction have a relatively small effect on the power to predict radon levels in the dwelling (See Appendix C).

Distributions of cumulative radon exposure by attained age for cases and controls are given in Appendix E for the disease groupings all leukaemias and for all other cancers. As in the case of the analagous distributions for gamma-rays, there is the expected tendency for higher doses to have been accrued by those diagnosed at older ages.

Appendix E shows the distribution of cumulative radon exposure by Carstairs quintile. In contrast to the gamma ray results there is a marked tendency for the more affluent groupings to have higher radon levels.

4.3 The possible influence of migration

The radiation and SES estimates used in this study have been assigned on the maternal residence at the time of birth of the study participant. If the study participant moves house between birth and the time when the cancer is induced ("migration") a less accurate estimate of radiation exposure and area based SES will be made. In general, investigators (Raaschou-Nielsen *et al* 2008; UK Childhood Cancer Study Investigators 2000) have attempted to achieve a full residential history including all homes occupied by the individual between birth and diagnosis, or at least a residential history of all homes occupied for a significant period (eg six months). It should be noted that even so there is uncertainty about the appropriate period to consider because of uncertainty in the latent period.

Table 3.2 shows that (for all childhood cancers together) address at diagnosis is the same as address at birth for about half the cases included in the analysis. This is broadly consistent with the findings of the UKCCS (UK Childhood Cancer Study Investigators 2000) which reported that 7629 control families (p 1081) had lived at a total of 12757 addresses (Table 12: the total being limited to addresses occupied for six months) so the mean number of addresses occupied for more than six months by controls was 12757/7629 or about 1.67. This would be consistent with half the participants having moved once and a small proportion more often. In terms of distance moved from the address at birth, as noted above, about half the cases had not moved at all and a further 20% had moved less than 2 km; 80% had moved less than 5 km. A minority had moved long distances. The mean distance between the address at birth and that at diagnosis was about 30 km for cases who had moved and about 16 km for all cases.

Table 3.3 gives data broken down by age at diagnosis of the number of cases which were still resident in the County District of birth at the time of diagnosis. For all childhood cancers taken together 96% of those diagnosed in the first year of life were still in the County District in which they were born. This figure dropped to 75% for those diagnosed at age 14. For all ages the figure was 83%. As with the distance between address at birth and at diagnosis, the figures for leukaemia are similar to those for all childhood cancers taken together.

There is no doubt that better estimates of radiation exposures and of SES could be made if full residential histories were available for study participants. However, examination of the data shows that the scale of migration is smaller than might be feared. Moreover, the effect will be some reduction in power rather than introduction of bias. We further note that, despite having set out to collect residential histories (UK Childhood Cancer Study Investigators 2000), the UKCCS investigators analysed in terms of gamma-ray dose rate (UK Childhood Cancer Study Investigators 2002b) and radon concentration (UK Childhood Cancer Study Investigators 2002a) at a single address, that occupied at diagnosis.

4.4 The possible influence of overmatching between cases and controls

A case is matched with one or two controls from the same birth register and the maternal residential address at birth of a control will therefore in general be reasonably close to that of the matched case. This will increase the chance that cases and controls are assigned the same estimate of radiation exposure or Carstairs value ("overmatching"). This is quantified in Table 3.4. The mean separation between the maternal residential address at birth of cases and that of their matched controls is about 11 km. This figure does not vary significantly with diagnostic grouping. About half of the controls had a maternal residential address at birth more than 7 km from that of the matched case.

The effect of overmatching will be greatest for gamma ray exposures since these are assigned on the basis of larger geographical areas than radon estimates or Carstairs scores. As noted in Section 3, the result of overmatching is that about half of study subjects (52% of all cases; 48% of all controls) have the same estimated gamma ray dose rate as their matched control/case. As with migration, the effect will be to diminish the power of the study, but will not introduce appreciable bias (see above). The effect of overmatching could be reduced if gamma ray estimates were available for smaller areas.

4.5 Trends of childhood cancer with natural radiation dose

4.5.1 The separate analyses that have been undertaken

In our main analysis (Table 3.9, and in simplified form Table 4.1) we find an association between time-integrated gamma ray exposure and all childhood cancer which is significant at the 5% level (two sided test). The relative risk (RR) is 1.03, 95% Confidence Interval (CI) 1.00-1.07, p=0.04. This is largely driven by the contribution from childhood leukaemia for which the association is somewhat larger and more significant than for childhood cancers a whole (RR=1.09, CI=1.02-1.17, p=0.01). Within the subtypes of leukaemia, lymphoid leukaemia, the largest grouping, also shows a significant association (RR=1.10, CI=1.02-1.19, p=0.01). Other disease groupings in Table 3.9 which show significant elevation of the RR do so because of the contribution from leukaemia. Some other malignancies, in particular other types of leukaemia, show elevated RRs but the numbers of cases are smaller and the findings are not close to statistical significance.

Figure 4.1 shows smoothed RR by dose group with fitted trend lines for all leukaemias combined. Figure 4.2 gives similar data for all cancers other than leukaemia. There is a progressive increase in leukaemia excess risk with dose, which excess is always positive, and statistically significant for doses greater than 4.1 mGy. Although there are substantial uncertainties, the pattern for other cancers is somewhat different, with the RR slightly and non-significantly less than one up to about 12 mGy, above which there is a progressive increase in risk; because of the much greater leverage of the high dose points this upturn at relatively high dose results in a non-significant positive trend.

In a study of 2165 cases and 5086 matched controls the UKCCS investigators found no association between natural gamma exposures and childhood cancer (UK Childhood Cancer Study Investigators 2002b). However, the investigators noted that this might be a consequence of limited statistical power. The power calculations of Little et al (Little *et al* 2010) confirm that this study was indeed underpowered. Geographical correlation studies have generally not reported an association between childhood cancer and environmental gamma radiation (Alexander *et al* 1990; Gilman and Knox 1995; Muirhead *et al.* 1991; 1992)

The RRs in Table 4.1 for associations between time integrated radon exposure and all childhood cancer, leukaemia and lymphoid leukaemia are 1.08, 1.12 and 1.24 respectively. These are all elevated, but none is close to statistical significance; nor are the RRs for any other of the listed malignancies. A number of published epidemiological studies have suggested an association between exposure to radon and various types of childhood leukaemia. For example, a national record based case control study in Denmark reported that cumulative radon exposure was associated with risk for acute lymphoblastic leukemia (ALL), with rate ratios (compared to a low exposure group) of 1.21 (0.98 –1.49) for an intermediate exposure group and 1.63 (1.05–2.53) for a high exposure group, but not with acute myeloid leukaemia (AML) (Raaschou-Nielsen *et al* 2008). These authors suggested that 9% of childhood ALL cases in Denmark could be attributed to residential exposure to radon, although the CI for this attributable proportion is wide. A national geographical correlation study in France reported a highly significant association between indoor radon concentration and incidence of AML ($P = 0.004$), but not for ALL (Evrard *et al* 2005). Our results are consistent with such associations, but the CIs on our results are wide enough for the results also to be consistent with no effect. For childhood leukaemia, the power of these studies to detect the predicted effect of radon is low, and the findings are compatible with the predicted effect. Given the low power of the studies, it is possible that the statistically significant associations reported for radon and childhood leukaemia result from chance fluctuations rather than indicating any underestimation of the leukaemogenic effect of radon.

Table 3.9 has included Carstairs Quintile as an estimate of SES in the analysis. Table 3.10 explores the effect of using the estimate of social class based on father's occupation as shown on the birth record. The RRs are similar to those of the main analysis, but the p values are generally a little higher. There is strong evidence that SES affects childhood cancer rates, particularly childhood leukaemia rates, in the UK (Kroll *et al* 2011b). This is discussed in the introduction to this report see also COMARE's eleventh report (COMARE 2006) (section 3.29 and Tables 3.4a and 3.5a.) We therefore attach most weight to analyses that adjusted for SES. We preferred analyses using Carstairs Quintiles to father's social class as derived from his occupation as given on the birth record because the latter was incomplete and based on self-reported information.

Table 3.11 is the same as the main analysis of Table 3.9, but using Carstairs scores rather than quintiles of the distribution of Carstairs scores. The results for gamma rays are almost the same as in the main analysis; for radon, the RRs are generally similar to those of the main analysis but perhaps a little lower.

Table 3.12 explores the effect of omitting any SES indicator from the analysis. The RRs are similar to those of the main analysis, but the p values for the gamma ray analyses are generally a little higher.

It is reassuring that the results in tables 3.10, 3.11 and 3.12, summarised in Table 4.2, demonstrate that the findings for gamma rays and for radon are not significantly dependent on the treatment of SES in the model.

Table 3.13 presents results for analyses like those of Table 4.1 but for cumulative radon exposure without gammas and for cumulative gamma exposures without radon. In both cases the model also included Carstairs Quintile. For both gamma ray and radon exposures the RRs and their significance in these separate analyses are similar to those in the main analysis which included both radiation variables. As noted above, the correlation between estimated gamma and radon exposures of cases and controls is weak and the results of Table 3.13 confirm that the main results are not influenced by any interaction between the radiation variables.

Table 3.14 is similar to Table 4.1 but is restricted to case-control sets which had GridSquare/AP estimates of radon exposure. These GridSquare/AP estimates are likely to be more precise than the other radon estimates described in section 2. The numbers of cases are somewhat smaller than in Table 3.9 and, while the RRs are generally similar, only those for time integrated gamma ray exposure and all leukaemia and lymphoid leukaemia reached statistical significance. As discussed in Section 2 we decided before the analysis was undertaken that most weight should be attached to the analysis including all types of radon estimate since the somewhat greater reliability of the GridSquare/AP estimates was likely to be outweighed by the smaller numbers of cases and controls if the analysis were restricted in this way. The results of Table 3.14 do not suggest that significant effects of radon exposure were going undetected because of the inclusion of less precise estimates of radon exposures in Table 3.9.

Table 3.15 is similar to the main results Table 3.9 but is based on results in which alternative estimates of radon concentrations in the homes of study participants have been used. In all other tables the radon estimates are from the HPA/BGS predictive map; in Table 3.15 they are means for the County District in which the birth address of the study participant is located. In this analysis the RRs for radon tend to be closer to one than in the main analysis; the RRs for gamma rays are virtually unaffected. In the main analysis the association between childhood cancer and radon exposures is suggestive rather than significant. The less marked association with radon in this analysis might be a consequence of cruder estimates of radon exposure. The unchanged results for gamma rays indicate that this part of the analysis is not affected by radon.

Table 4.3 summarises the gamma ray results for analyses in which different radon estimates were employed. It can be seen that the gamma ray results are not sensitive to the choice of radon estimator.

Table 3.16 presents results for gamma ray dose rate and radon concentration rather than time integrated quantities. None of the RRs are significantly raised. This analysis also throws light on the effects of *in utero* exposures since the *in utero* dose will be proportional to the exposure from gamma rays or radon incurred over the nine months

of pregnancy. Studies of obstetric radiography (Bithell and Stewart 1975; Stewart *et al* 1956) have suggested that both leukaemia and other childhood cancers could be induced by *in utero* exposure to a similar extent, although there is only weak evidence for an excess of childhood solid cancers and none for leukaemia in the Japanese atomic bomb survivors exposed *in utero* (Wakeford and Little 2003). Nonetheless, the excess relative risk coefficient for childhood leukaemia obtained from the Japanese atomic bomb survivors exposed postnatally is compatible with that for *in utero* exposure derived from the Oxford Survey of Childhood Cancers, although uncertainties are substantial (Wakeford and Little 2003). Wakeford and Little (Wakeford and Little 2003) proposed that the ERR coefficient for both childhood leukaemia and childhood cancers other than leukaemia following exposure *in utero* is around 50/Sv, so that an average dose of about 0.5 mSv received from natural background radiation between conception and birth would lead to an ERR of childhood cancers other than leukaemia of about 2%. A very large study would be required to detect this small effect. In our data there is little indication of an association for childhood cancers other than leukaemia, though the CIs are large and consistent with some effect.

Table 3.17 presents tests for associations between estimates of red bone marrow (RBM) dose and leukaemia (this dose quantity is unlikely to be relevant to most other childhood malignancies). In the analyses for radon and gamma rays separately, the p values are, of course, identical to thos of the main analysis. However, the results in this table, in terms of risk per mSv, can be compared with risk estimates from other sources of information on leukaemogenesis from childhood irradiation. This is discussed below. For the analysis in terms of total red bone marrow (RBM) dose from gamma rays and radon combined the results are generally similar to those of the gamma ray analysis. There are considerable uncertainties in estimating the dose to red bone marrow from radon but it is estimated that it is about an order of magnitude smaller than that from gamma rays (Kendall *et al* 2009). The results in this table are similar to those of the main analysis and we would not attach any weight to the differences.

Table 3.18 gives a breakdown for males and females separately using the approach of Table 3.9. The numbers of cases are, of course smaller and the results, while similar to those of the main analysis are less significant. For females, none of the RRs are elevated to a significant extent. However the differences between RRs for males and for females are generally small and the heterogeneity in RR by sex is not generally statistically significant (Table 3.24). The analysis for trend of “Other leukaemia” with integrated radon exposure is an exception, but this may be a chance result. As expected (Stiller 2007) there are rather more cases of childhood cancers in boys than in girls, with the disparity differing somewhat between diagnostic groups.

Tables 3.19 and 3.20 give a breakdown by four age groups: less than 1 year, 1-4 years, 5-9 years and 10-14 years at diagnosis. Again the numbers are smaller than in the main analysis. However, on the basis of the numbers available, the elevated RRs for leukaemias appear to be concentrated in the age group 5-9 years and, to a lesser extent 10-14 years. For radon, differences in radon RR across the four age groups reach formal statistical significant for two disease groupings (Non-Hodgkin lymphoma and total lymphoma), see Table 3.24. However, these may well be chance results. A formal test of heterogeneity of the variation of leukaemia relative risk has p=0.967 and

p=0.713 for gamma and radon respectively. Likewise, for all other cancers a formal test of heterogeneity of the relative risk coefficient has p=0.208 and p=0.864 for gamma and radon respectively.

Table 3.21 explores the age variation of the RRs for total leukaemia and for lymphoid leukaemia by single year of age at diagnosis. Random uncertainties play a greater role in this more detailed breakdown and the data should not be overinterpreted. No particular pattern is suggested by the radon results. There is little evidence for heterogeneity between the RR for single years of age at diagnosis (Table 3.24); we do not attach any significance to the heterogeneity in gamma ray RR for the disease grouping "other malignant tumours". However, taking a broader view, in the gamma ray analysis for lymphoid leukaemia there is perhaps a suggestion of increased RR between ages at diagnosis 5 and 12 or so with a peak around 9 years of age. It is possible that the peak at 2-4 years may result from in-utero effects and that a later peak reflects a balance between decreasing radiosensitivity and cumulative dose as age increases.

Tables 3.22 and 3.23 give results using different assumptions about the appropriate latent period for induction of childhood cancer. Table 3.22 presents results for 0 and 9 months and Table 3.23 for 12 and 24 months. The second panel (9 month latency) in Table 3.22 is given for convenience; the results are the same as those of the main Table 3.9. Unsurprisingly, the results for latent periods 9 and 12 months are almost identical. Those for 0 and 24 months are very similar. Table 4-3 summarises these comparisons for the gamma ray analyses.

4.5.2 Summary of the analyses

The most striking feature of the results of the analyses described above is an association between lymphoid leukaemia and cumulative gamma ray exposure which is significant at around the 0.01 level. It is seen in the main analysis (Table 3.9), which includes gamma ray and radon exposures integrated from the time of conception to nine months before diagnosis and Carstairs Quintile as a measure of SES. Similar results are seen in analyses which use alternative measures of SES: Carstairs score rather than quintile, father's social class as implied by occupation given on the birth certificate or no allowance for SES (Table 4.2). The absence of an effect of adjustment for SES implies that the relative risks of gamma ray exposure are similar across SES categories. The gamma ray results are essentially unaffected by the use of an alternative method for estimating radon exposures, by omitting radon from the model or by restricting the analysis to case control sets which had radon estimates based on gridsquare mapping and addresspoint locations for the places of birth (Table 4.3).

The results of this study are insensitive to the alternative assumptions that were made about the appropriate latent period (Table 4.4). Results were similar whether exposures were integrated from conception to diagnosis or from conception to 9, 12 or 24 months before conception.

The results of our main analysis are compatible with predictions based upon conventional dosimetry and risk modelling that radon plays a minor role in the induction of childhood leukaemia, but the CIs are wide enough to be consistent with the possibility

of no effect of radon exposure on childhood leukaemia risk. This picture is reinforced by our subsidiary analyses. In particular, the results of the main analysis are similar to those in which the effects of gamma rays and of radon are combined by analysing in terms of the estimated dose to the red bone marrow (RBM) from both sources combined (Table 3.17). Estimated RBM doses from radon are lower than those from gamma rays by approaching an order of magnitude and power calculations based on these doses suggest that very large studies are required to detect the predicted risk (Little et al 2010).

Our results (Table 3.18) do not, in our view, provide evidence for any significant difference between males and females for the induction of childhood cancer by radiation. The evidence on risk with age is more suggestive of genuine variation (Tables 3.19, 3.20). This applies in particular to the induction of lymphoid leukaemia by gamma rays (Table 3.21). In the analysis by single year of age at diagnosis, only one point, at age 9, is significantly elevated (p=0.04). However, the adjoining points are somewhat elevated and there is a suggestion of a peak in the RR between ages at diagnosis 5 and 12 or so. If real, such a peak might reflect a balance of accumulation of post-natal exposure against a sensitivity which reduces with age at exposure. This variation of risk with attained age follows the same pattern as the BEIR VII model predictions.

Studies of obstetric radiology (Bithell and Stewart 1975; Stewart *et al* 1956; Stewart *et al* 1958) suggest that both leukaemia and other childhood cancers could be induced by *in utero* exposure. There is little evidence for an excess of solid cancers and none for leukaemia in the Japanese atomic bomb survivors, however, the excess relative risk coefficients are compatible with those in the obstetric studies (Wakeford and Little 2003). Our analysis in terms of gamma ray dose rate and radon concentration rather than time integrated quantities (Table 3.16) examines the effect of *in utero* exposures since the *in utero* dose will be proportional to the exposure from gamma rays or radon incurred over the nine months of pregnancy. Of course, all our cases, except those diagnosed very shortly after birth, will have been exposed to both *in utero* and post-natal irradiation and distinguishing the effects of the two is not easy. The results of Table 3.16 are broadly similar to those of the main analysis though none of the RRs are significantly raised. In our data there is thus no clear indication of an association for childhood cancers other than leukaemia, though the CIs are large enough to be consistent with some effect.

Doll and Wakeford (Doll and Wakeford 1997) suggested that, in contrast to childhood leukaemia, the cells sensitive to radiation-induction of the typical cancers of childhood are active throughout pregnancy but less so after birth. The implication is that it is only exposure to natural background radiation *in utero* that would materially increase the risk of the common cancers of childhood other than leukaemia. In contrast childhood leukaemia would be predicted to be induced by both exposure *in utero* and after birth.

4.6 Compatibility of the risk estimates found here with published values

Table 2 of Wakeford et al (Wakeford *et al* 2009) shows that about 15% of childhood leukaemia incidence is attributable to ~1 mSv/year red bone marrow dose from natural background. This estimate is based on the UNSCEAR 2006 (UNSCEAR 2008) risk models with the 70%ERR, 30%EAR transfer model, averaging over sexes and including *in utero* dose. This means that the relative risk at 1 mSv/year is about 1.15. Our Table 3.17 which is in terms of mSv gives an RR for total leukaemia of 1.12 (1.03 to 1.22) for gamma rays. Taking this as a relative risk, it is slightly lower than the UNSCEAR model prediction. But the two are likely to be compatible taking into account uncertainties in the UNSCEAR model predictions and the probable depression of our RR resulting from approximate estimates of radiation doses.

Table 4.5 presents a more detailed comparison by age of the risks observed in this study with those predicted by the UNSCEAR (UNSCEAR 2008) and BEIR (National Research Council (NRC) 2006) models. Cumulative incidence risks predicted by the relative risk model estimated here, and assuming 1 mGy / year, are generally somewhat higher than those predicted by the BEIR VII model, but until age 5 lower than those predicted by the UNSCEAR 2006 model. Above that age predicted risks exceed those of the UNSCEAR model. By age 15 risks are about 2-2.5 larger than those predicted by the UNSCEAR and BEIR VII models, although there are substantial uncertainties in all estimates.

Little (Little 2008) presented excess relative risks for leukaemia (with an allowance for cell killing) in childhood radiation therapy studies (Tables 1, 3). The ERR are in the range 2-14 per Sv, slightly lower than the ERRs that can be estimated from the Japanese atomic bomb survivors exposed in childhood (10-20 per Sv). Using the range 2-14 per Sv the risks are equivalent to an ERR of 0.01 to 0.07 per 5 mSv (the mean age at diagnosis in our study is about 5 years). These ERR are for the whole of life. Taking them to apply to childhood cancer is an crude approximation. However, these risks are broadly compatible with our study, given that there are large CI on the results of the medical studies.

4.7 Interpretation of the findings of the present study

One of the strengths of the case-control study reported here is that its results can be interpreted in the light of previous assessments of the role of natural background radiation exposure in the incidence of childhood leukaemia. Based upon recent dosimetry and risk modelling, these calculations imply that some 15% of cases of childhood leukaemia in Great Britain may be attributable to this source of radiation exposure, although uncertainties on this estimate are substantial. Power calculations taking account of the geographical variation of external gamma ray and radon exposures in Great Britain suggest that the predicted risk attributable to gamma ray exposure could be detected with a reasonable level of probability by a national case-control study of a size that is practicable to conduct, at least using a record-based design. The size of the present national case-control study approaches that indicated

by the power calculations. Therefore, the case-control study offers the opportunity to realistically test the predicted radiation-induced effect, and the association between childhood leukaemia and gamma ray exposure must be viewed with this in mind.

In the following sections we consider the possible interpretations of the statistically significant association between childhood leukaemia risk and the cumulative RBM dose received from naturally occurring gamma radiation.

Chance

The play of chance can never be absolutely excluded as a possible explanation for a statistically significant association found in an epidemiological study. However, the results of the study reported here must be judged against the prior calculations of the power of epidemiological studies investigating the relationship between childhood leukaemia and natural background radiation. On the basis of these calculations, this case-control study has a reasonable probability (~50%) of detecting the predicted level of excess risk of childhood leukaemia arising from ubiquitous exposure to natural background radiation, in particular external gamma ray exposure. In this context, the statistically significant association between childhood leukaemia and naturally occurring gamma ray exposure can be interpreted more confidently as representing an effect other than chance as opposed to the many associations found in epidemiological studies that are not set against such a backdrop of prior assessment, prediction and power calculations.

In contrast to the statistically significant association between exposure to gamma radiation and childhood leukaemia is the absence of a significant association for childhood cancers other than leukaemia and gamma radiation, and the lack of significant associations between exposure to radon and either childhood leukaemia or childhood cancers other than leukaemia. As with leukaemia, the typical cancers of childhood other than leukaemia may be caused by radiation exposure *in utero*, but unlike leukaemia, the evidence for postnatal exposure increasing the risk of these cancers is limited, so the power to detect the influence of gamma radiation from natural sources upon the risk of these cancers is materially lower than that for childhood leukaemia. Also, the dose to the RBM from radon (and almost certainly the dose from radon to other target tissues of relevance to childhood cancers) is substantially lower than that from gamma radiation, so the power to detect the predicted radon-induced risk of childhood leukaemia (and other cancers) is much lower than that for childhood leukaemia and gamma-rays. As a consequence, the pattern of associations found in this study is consistent with the predictions founded on prior evidence, which encourages the inference that the statistically significant association between childhood leukaemia and gamma radiation from natural sources has an explanation other than chance.

Bias

This is a record based case-control study that does not require the active participation of study subjects and is therefore free of the participation or selection bias that can pose serious difficulties in the accurate interpretation of the findings of some case-control studies. Cases and controls were those children affected by cancer and matched

unaffected children, details of which are held by the National Registry of Childhood Tumours, which is an essentially complete dataset for all childhood cancer cases in Great Britain (Appendix B). For each case, one or two controls had already been selected from the same birth register as the case, matched on sex and date of birth (to within six months). It is difficult to envisage how serious selection bias could arise under these circumstances. About half the cases in this study were assigned the same gamma ray dose rate as their control(s). However, although this reduces the power of this aspect of the study, which is undesirable but presently unavoidable, it should not lead to the introduction of bias. For each study subject data on radiation exposures and socio-economic status were obtained from pre-existing databases independent of case or control status, which excludes information bias. As noted above, the use of areal averaged exposures applied to individual study subjects should not lead to the introduction of material bias.

Although it is impossible to demonstrate the exclusion of all sources of bias from a case-control study, the design of this study is such that the influence of serious bias should have been avoided. The more frequent sources of bias that affect case-control studies have been examined above, and it is unlikely that they are present to any meaningful extent in this study.

Confounding

The known risk factors for childhood leukaemia are few (Belson *et al.* 2007). Ionising radiation is an established risk, as are certain familial genetic syndromes (see Ziegelberger et al (Ziegelberger *et al.* 2011) for a review). There is increasing evidence that infection plays an important part in childhood leukaemia. Two principal hypotheses have been proposed: that childhood leukaemia is a rare response to a common, but as yet unidentified, infection (the “Kinlen hypothesis” (Kinlen 1988; 2011), and that delayed exposure to a range of general infections increases the risk of childhood leukaemia (the “Greaves hypothesis” (Greaves 2006a; 2006b; Greaves 1988; Greaves and Chan 1986). A considerable body of evidence supports the idea that population mixing is associated with childhood leukaemia (Kinlen 2011). The growing evidence that the risk of childhood leukaemia is raised by increasing socio-economic status (Kroll *et al* 2011b) (COMARE 2006) may well be related to different patterns of infections in different socio-economic groups.

The association between the risk of childhood leukaemia and higher socio-economic status is confirmed by the analyses conducted as part of this study. However, adjusting for socio-economic status using two measures, one community based and the other individual based, does not affect the association with gamma ray exposure. Further, the matching of cases and controls by birth register controls for any variation of risk factors by area of birth. Accounting for socio-economic status and area of birth in this study reduces the influence of any major confounding non-radiation risk factor upon the association between childhood leukaemia and gamma ray exposure. As such the scope for confounding is probably minimal, although, as in epidemiological studies generally, it is impossible to prove that it could not arise.

We now consider potential confounders for the main other type of haemopoietic neoplasms, Hodgkin's lymphoma (HL) and non-Hodgkin lymphoma (NHL). In order to ensure that relevant factors are not overlooked the evidence that we briefly survey is not specifically related to childhood exposure or to the childhood period of expression of risk. HL is associated with Epstein-Barr virus (Thomas *et al.* 2002) and with HIV (Swerdlow 2003), and elevated risks are also seen among allogeneic bone-marow transplant patients (Swerdlow 2003), all suggestive of a role for the immune system for this tumour. About 5% of HL cases are thought to be of genetic origin (Swerdlow 2003). NHL is associated with chronic immunosuppression (Hoover and Fraumeni 1973; Kinlen 1985), and as with HL also with Epstein-Barr virus (Mueller *et al.* 1992) and HIV (Serraino *et al.* 1992), again all strongly suggesting a role for the immune system in the aetiology of this tumour. Neither HL nor NHL are strongly radiogenic (UNSCEAR 2008), somewhat confirmed by the results of this paper (Table 3.9). Given the largely immunogenic phenotype of both tumours, confounding is unlikely.

The main solid tumour subtype in childhood is brain/CNS cancer. As for leukaemia, ionising radiation is the main exogenous risk factor for these tumours (Little *et al.* 1998; Ron *et al.* 1988; Shore *et al* 1993; Taylor *et al.* 2010; UNSCEAR 2008). Again, the evidence that we consider is not specifically related to chilhood exposure or to the childhood period of expression of risk. There is consistent evidence from a number of childhood-exposed groups that malignant brain tumours (in particular gliomas and primitive neuroectodermal tumours, PNET) have markedly lower excess relative risk per unit dose than do benign tumours (in particular meningiomas and schwannomas) (Little *et al* 1998; Sadetzki *et al.* 2005; Taylor *et al* 2010); the same is true for exposure at older ages (Preston *et al.* 2007). There are elevated risks from certain specific types of chemotherapy for certain types of CNS tumours; in particular intrathecal methotrexate, used in treatment for cancer in childhood, has been suggested as a risk factor for meningioma (Taylor *et al* 2010). In the absence of radiation exposure, males have a somewhat higher risk than females (Stiller 2007) of childhood tumours of the brain and CNS. There is also an inverse association between asthma and allergy and brain cancer (Brenner *et al.* 2002; Schlehofer *et al.* 1999; Wiemels *et al.* 2004; Wiemels *et al.* 2002), suggesting a role for the immune system in the aetiology of this tumour. There is also a (small) role for specific genetic syndromes, in particular neurofibromatosis type 1 (Gurney *et al.* 2001; Little *et al* 1998), tuberous sclerosis, nevoid basal cell syndrome, and Li-Fraumeni syndrome (Lindor *et al.* 1998). As for leukaemia, it is unlikely that there is marked counfounding of the dose response for brain/CNS cancer.

There is plausible evidence that therapeutic irradiation of children with the heritable form of retinoblastoma, carrying a mutant *RB1* allele in the germline, causes the subsequent development of second primary tumours (SPT) under the age of 15 years. In one of the few cohorts of such children studied (MacCarthy *et al* 2009) high rates of SPT were seen, with a particularly high proportion of osteosarcomas occurring in childhood, 18 out of 31 SPT. Most children in this cohort with heritable retinoblastoma would have received therapeutic irradiation, but it is not stated how many of the SPT occurred within the irradiation field. These children have a genetic constitution which might render them unusually sensitive to irradiation, but it seems that therapeutic irradiation doses can cause further childhood cancers of different types in them. The population prevalence of *RB1* heterozygotes is about 2×10^{-5} (Czeizel and Gárdonyi

1974; Fitzgerald *et al.* 1983; Little *et al.* 2012). Since the population cumulative incidence of childhood leukaemia (from birth) is about 6×10^{-4} for both sexes (Office for National Statistics 2001) this implies that the vast majority of NRCT leukaemia cases could not be *RB1* heterozygous – in particular there is almost no scope for confounding of dose response.

Cause-and-effect

The other interpretation of the statistical association between childhood leukaemia risk and the dose of gamma radiation from natural sources is that it represents cause and effect. It is beyond reasonable doubt that moderate and high doses of radiation delivered at a high dose-rate increase the risk of childhood leukaemia (and it is upon the experience of the Japanese atomic bomb survivors that the risk models used for our power calculations are based). However, the generalisation to low doses delivered protractedly is less generally accepted. It is, of course very difficult for an epidemiological study to detect the small relative increase in risk that is predicted to be produced by low level exposure to radiation against statistical fluctuations in background risk and the potential influence of subtle biases and confounding factors. Nonetheless, evidence does exist that low doses and low dose-rates of radiation do increase the risk of (at least some types of) cancer at around the level predicted by conventional risk models, and this evidence embraces childhood leukaemia. Moreover, radiobiological arguments point in the same direction.

Set against this background and the absence of indications of a significant influence of bias or confounding, we are inclined to the conclusion that the statistical association between childhood leukaemia and exposure to gamma radiation from naturally occurring sources that has been found in this case-control study represents a causal relationship. Uncertainties in the leukaemia risk coefficients implied by the association and the comparison with predicted values are substantial, but the findings of this study are consistent with the risk models that currently form the foundations of radiological protection and, in particular with the extrapolation to the milli-Sievert range of radiation risks observed at higher doses.

5 SUMMARY AND FUTURE STUDIES

We have conducted a record based case/control study of childhood cancer and two components of natural radiation exposure: indoor gamma rays (with the directly ionising component of cosmic rays) and radon. The study is larger than any other case-control study on this topic of which we are aware and includes 27447 cases of childhood cancer and 36793 controls. These were from the National Registry of Childhood Tumours. The radiation exposure of cases and controls was estimated using identical methods. Gamma ray dose rates were assigned on the basis of the County District in which the mother was living at the time of birth of the child. Radon concentrations, for the address of the mother at the time of birth of the child, were estimated from a predictive map which was based on more than 400,000 radon measurements and which also took into account geological boundaries. Before the analyses were undertaken it was decided that the main analysis, ie that to which most weight should

be given, would consider time integrated radiation exposures for the period from the birth of the child to diagnosis of the cancer (roughly equivalent to the period from conception to nine months before diagnosis). Socioeconomic status (SES), as quintiles of the distribution of the Carstairs index of deprivation, was included in the analysis. The main endpoints of interest were ALL, all leukaemias and all childhood cancers. Subsidiary analyses considered other endpoints and variants of the main analysis.

Alternative analyses were conducted using

Alternative measures of SES

Carstairs scores rather than quintiles,

Fathers social class derived from his occupation as given on the childs birth certificate or

With no allowance for SES.

Alternative estimates of radon exposures

Mean values for County Districts

Restriction to the subset of estimates likely to be the most precise

Gamma ray dose rates or radon concentrations rather than time integrated quantities

Estimates of the dose to the red bone marrow from gamma rays and radon combined (for leukaemia only)

The study has formidable advantages: it is of exceptional size and the inclusion of all records from an essentially complete register of cases (with matched controls) means that participation bias, so often a problem for case/control studies does not arise. The study design carries with it one unavoidable disadvantage: the fact that individual contact was not made with study participants means that radiation levels and SES variables have been estimated as the average for the area in question rather than being directly measured in the homes of those concerned. In the case of the radon estimates the areas are small, but for gamma rays they are County Districts of which there are 459 in Great Britain. There is a degree of geographical matching on the place of birth of cases and controls, which raises the possibility that radiation estimates for the two will be the same. This arises very rarely in the case of radon estimates, but approaching half the cases have the same gamma ray estimate as their controls. This will reduce the power of the study somewhat, but will not introduce bias.

A further disadvantage imposed by the data available to the National Registry of Childhood Tumours is that full residential histories for cases and controls are not available. Address at birth is known for cases and controls and address at diagnosis for cases. The analysis has therefore assigned radiation levels on the basis of the address at birth. Again, the effect of study participants moving from the birth address will be to weaken the power of the study somewhat, but not to introduce bias.

It can never be proved that confounding by some unexpected and unidentified mechanism is impossible. However, we are unable to identify any mechanism by which

such confounding might plausibly account for the observed magnitude and specificity of effects in this study.

The present study has the considerable advantage of following an estimation of the predicted risk of childhood leukaemia arising from natural sources of radiation based upon the most recent leukaemia risk models and the distribution of RBM doses within the British population of children (Little *et al* 2009; Wakeford *et al* 2009). There has also been an investigation by Little et al, using the same risk models and RBM dose estimates of the size of various type of epidemiological study that would be required to have a reasonable chance of detecting an association between natural background radiation and childhood leukaemia (Little *et al* 2010). A power calculation, based on the same methods as those of Little et al (Little *et al* 2010) indicates that this study has a power of about 50% to detect an association between gamma ray exposure and childhood leukaemia.

The most striking finding of this study is an association between lymphoid leukaemia and cumulative gamma ray exposures which is significant at around the 1% level. Results for all forms of leukaemia combined are similar, but are clearly dominated by the contribution from lymphoid leukaemia. These findings are exceptionally robust as regards alternative assumptions about the treatment of the radon or the SES quantities. The relative risk that we have found appears to be consistent with other estimates of the risks of radiation induced childhood cancer (National Research Council (NRC) 2006; UNSCEAR 2008). We believe that the elevated relative risks which we have found are likely to reflect a real effect of natural radiation on leukaemia rates. Our study therefore provides support to the assumption that radiation risks observed at higher doses may be extrapolated down into the milli-Sv range at about the level predicted from other data, in particular the survivors of the atomic bombs.

A weaker association between childhood cancer and radon exposure is suggested by our results but is not demonstrated as statistically significant. This is what might be expected on the basis of dosimetric arguments (Little *et al* 2010). Our results are consistent with an association between childhood leukaemia of about the size that would be suggested by dose calculations and with positive associations reported in some other studies, for example, that of Raaschou-Nielsen (Raaschou-Nielsen *et al* 2008). However, the confidence intervals on our results are wide enough for the results also to be consistent with no effect

5.1 Future studies

It would be highly desirable to conduct a further analysis using individual gamma ray dose estimates, or estimates for areas smaller than County Districts. Plans to develop such estimates are in hand.

While we find our results compelling, it would be desirable to test associations between natural radiation exposures and childhood cancer using independent datasets. The results of this study indicate that it is not essential to have the most accurate information on the mothers residence at the time of birth of the child. Analyses using the location of the postcode in question gave similar results to those where the more precise

Addresspoint was used. We therefore propose to include births in Great Britain from 1962 to 1979 in a future analysis. Other independent confirmation would require data from other countries.

Analyses of a larger dataset with better gamma ray estimates will allow

1. For gamma rays
   a Confirmation of the association with childhood leukaemia
   b Refinement of the relative risk and hence risk factor for leukaemia
   c Refinement of the relative risks for other diseases
   d More evidence of the possibility of a peak in leukaemia response around age 9
   e More evidence on possible differences in radiosensitivity between the sexes
   f More evidence on the most appropriate latent period
2. For radon
   a Refinement of the relative risks for different disease groupings

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8 TABLES

Table 1.1 Components of annual radiation dose to a 10Y old child

Doses in micro Sv from natural radiation sources. The columns are

a) (committed) effective doses from one years intakes by a 10Y old child

b) Mean actual annual RBM doses from conception to the fifteenth birthday

	Effective dose from one years exposure	Mean annual RBM dose at ages 0-14
Internal radionuclides in food	320	550
Radon and thoron	1400	100
Terrestrial gamma rays	400	400
Cosmic rays (directly ionising)	260	280
Cosmic Rays (neutrons)	90	90
Total	2500	1400
Contributions measured in epidemiological studies		
Terrestrial gamma rays with directly ionising cosmic rays	660	680
Radon	1300	80

Table 3.1. The study population

	Records meeting date criteria	Records with incomplete postcodes	Study population	Number with address point grid reference available	Number with code point grid reference only
Case	27854	407	27447	26457	990
Control 1	27784	407	27377	26334	1043
Control 2	9477	61	9416	9177	239
Total Controls	37261	468	36793	35511	1282
Total Records	65115	875	64240	61968	2272

Table 3.2 Distance between postcode of birth and of diagnosis for cases[a]

	Leukaemia (ICCC3 11-15)			Lymphoma (ICCC3 21-25)			Other diagnoses (31-122)			All Cancers		
Distance moved km	Number	Cumulative	%	Number	Cumulative	%	Number	Cumulative	%	Number	Cumulative	%
0	4423	4423	49	794	794	34	7927	7927	49	13144	13144	48
0-1	1262	5685	63	430	1224	53	2168	10095	63	3860	17004	62
1-2	665	6350	70	212	1436	62	1244	11339	71	2121	19125	70
2-3	406	6756	75	152	1588	69	791	12130	76	1349	20474	75
3-4	275	7031	78	110	1698	73	506	12636	79	891	21365	78
4-5	218	7249	80	61	1759	76	350	12986	81	629	21994	80
5-6	184	7433	82	49	1808	78	292	13278	83	525	22519	82
6-7	144	7577	84	45	1853	80	230	13508	84	419	22938	84
7-8	105	7682	85	27	1880	81	197	13705	85	329	23267	85
8-9	86	7768	86	23	1903	82	137	13842	86	246	23513	86
9-10	80	7848	87	23	1926	83	107	13949	87	210	23723	87
10-15	227	8075	89	73	1999	86	399	14348	89	699	24422	89
15-20	130	8205	91	34	2033	88	203	14551	91	367	24789	90
20-25	72	8277	92	19	2052	89	111	14662	91	202	24991	91
25-30	57	8334	92	14	2066	89	82	14744	92	153	25144	92
30+	706	9040	100	251	2317	100	1308	16052	100	2265	27409	100

Mean distance (km) between case birth postcode and case diagnosis postcode

	Number	Distance	Number	Distance	Number	Distance	Number	Distance
All cases	9040	14.8	2317	20.4	16052	15.2	27409	15.5
Cases that moved	4617	28.9	1523	31	8125	30	14265	29.8

[a]38 records are excluded from this analysis because the address at diagnosis is not known with sufficient precision

Table 3.3 Cases that moved from one County District to another between birth and diagnosis by age at diagnosis

Age (years) at diagnosis	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	0-14
All diagnostic groups (ICCC3 11-122)																
Did not move	2690	2087	1818	1454	1052	728	568	457	363	293	283	287	286	283	262	12911
Moved but in same CD	473	759	1072	1066	886	764	627	576	554	526	494	497	483	540	563	9880
Total in same CD	3163	2846	2890	2520	1938	1492	1195	1033	917	819	777	784	769	823	825	22791
(percentage)	96	92	87	84	82	81	79	78	77	75	74	73	76	73	75	83
Moved to different CD	140	256	445	486	415	348	323	286	267	270	270	291	248	299	274	4618
Total	3303	3102	3335	3006	2353	1840	1518	1319	1184	1089	1047	1075	1017	1122	1099	27409
Leukaemia (ICCC3 11-15)																
Did not move	554	665	797	707	452	301	194	154	90	95	82	71	73	55	39	4329
Moved but in same CD	104	241	460	482	397	283	220	172	148	136	123	118	100	104	120	3208
Total in same CD	658	906	1257	1189	849	584	414	326	238	231	205	189	173	159	159	7537
(percentage)	96	92	86	85	82	81	79	78	75	78	76	77	72	71	74	83
Moved to different CD	27	80	201	216	184	138	110	94	81	67	63	55	66	64	57	1503
Total	685	986	1458	1405	1033	722	524	420	319	298	268	244	239	223	216	9040
Lymphoma (ICCC3= 21-25)																
Did not move	18	30	41	63	85	74	65	63	46	35	44	43	50	68	58	783
Moved but in same CD	5	11	41	66	51	70	60	74	83	70	88	86	95	113	124	1037
Total in same CD	23	41	82	129	136	144	125	137	129	105	132	129	145	181	182	1820
(percentage)	100	87	90	82	79	83	81	78	81	74	75	76	81	70	75	79
Moved to different CD	0	6	9	28	36	30	30	38	30	36	44	40	34	76	60	497
Total	23	47	91	157	172	174	155	175	159	141	176	169	179	257	242	2317

Table 3.4 Distance (km) between postcode of birth for cases and their matched controls

	Leukaemia		Lymphoma		Other cancers		Total cancer	
	ICCC3 11-15		ICCC3 21-25		ICCC3 31-122		ICCC3 11-122	
Separation	Number	Cumulative percentage	Number	Cumulative percentage	Number	Cumulative percentage	Number	Cumulative percentage
0-1	632	5	169	5	1098	5	1899	5
1-2	905	13	265	13	1700	13	2870	13
2-3	1014	21	283	22	1886	22	3183	22
3-4	984	30	322	32	1743	30	3049	30
4-5	964	38	274	40	1624	37	2862	38
5-6	822	45	213	47	1488	44	2523	45
6-7	740	51	227	54	1334	50	2301	51
7-8	648	56	192	59	1178	56	2018	56
8-9	586	61	160	64	1076	61	1822	61
9-10	506	65	134	68	891	65	1531	65
10-15	1735	80	474	83	3186	80	5395	80
15-20	950	88	215	89	1663	87	2828	88
20-25	573	93	149	94	1034	92	1756	93
25-30	294	95	62	96	603	95	959	95
30+	559	100	135	100	1103	100	1797	100
Total	11912		3274		21607		36793	
Mean separation	11		11		11		11	

Table 3.5. Breakdown of cases by grouped age at diagnosis, sex and diagnostic grouping

Disease Grouping	ICCC3 Code	<1Y	1-4Y	5-9Y	10-14Y	All Ages	Mean Age
Lymphoid leukaemias	11	337	4182	1904	844	7267	5.1
Acute myeloid leukaemias	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 lymphomas	21	0	82	275	582	939	10.6
NHL except Burkitt lymphoma	22	14	273	371	325	983	7.8
All Lymphomas	21-25	23	468	803	1025	2319	8.9
Lymphoid leukaemia and NHL	11,22	351	4455	2275	1169	8250	5.4
Total leukaemia and NHL	11-15,22	703	5166	2654	1518	10041	5.3
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	18389	5.8
Total childhood Cancer	11-122	3311	11813	6955	5368	27447	5.6
Males							
Lymphoid leukaemias	11	156	2332	1114	483	4085	5.2
Acute myeloid leukaemias	12	125	266	163	150	704	5.5
Other leukaemias	13-15	60	113	50	42	265	4.7
Total leukaemia	11-15	341	2711	1327	675	5054	5.2
Hodgkin lymphomas	21	0	65	197	354	616	10.2
NHL except Burkitt lymphoma	22	10	168	276	209	663	7.9
All Lymphomas	21-25	15	321	595	660	1591	8.7
Lymphoid leukaemia and NHL	11,22	166	2500	1390	692	4748	5.5
Total leukaemia and NHL	11-15,22	351	2879	1603	884	5717	5.5
Brain and CNS tumours	31-36	303	1273	1202	762	3540	6.2
Other malignant tumours	41-122	1101	2142	829	848	4920	4.6
All Cancer except leukaemia	21-122	1419	3736	2626	2270	10051	5.9
Total childhood Cancer	11-122	1760	6447	3953	2945	15105	5.6
Females							
Lymphoid leukaemias	11	181	1850	790	361	3182	4.9
Acute myeloid leukaemias	12	112	255	125	120	612	5.0
Other leukaemias	13-15	55	77	41	37	210	4.6
Total leukaemia	11-15	348	2182	956	518	4004	4.9
Hodgkin lymphomas	21	0	17	78	228	323	11.3
NHL except Burkitt lymphoma	22	4	105	95	116	320	7.7
All Lymphomas	21-25	8	147	208	365	728	9.3
Lymphoid leukaemia and NHL	11,22	185	1955	885	477	3502	5.2
Total leukaemia and NHL	11-15,22	352	2287	1051	634	4324	5.1
Brain and CNS tumours	31-36	281	1078	1029	657	3045	6.3
Other malignant tumours	41-122	914	1959	809	883	4565	5.0
All Cancer except leukaemia	21-122	1203	3184	2046	1905	8338	5.8
Total childhood Cancer	11-122	1551	5366	3002	2423	12342	5.5

Table 3.6 Table of Carstairs Quintile against Fathers Social Class codings derived from occupation as given on the birth record.

Data are for cases and controls combined

	Social Class based on Fathers occupation as given on the birth certificate												
Carstairs	NoOccup	NoClass	Total Unset	1	2	3N	3M	4	5	Total Known	Total	%	%unset
1	221	124	345	1061	2739	1214	1535	661	127	7337	7682	12	5
2	350	151	501	933	2815	1256	2285	1067	259	8615	9116	14	8
3	578	199	777	893	2728	1425	3169	1524	424	10163	10940	17	12
4	1174	322	1496	838	2783	1580	4763	2368	866	13198	14694	23	23
5	2901	626	3527	693	2923	1851	6914	4083	1817	18281	21808	34	53
Total	5224	1422	6646	4418	13988	7326	18666	9703	3493	57594	64240	100	100
Percentage	8	2	10	7	22	11	29	15	5	90	100		
Percentage of known social class				8	24	13	32	17	6	100			

NoOccup are totals with no father's occupation given on the birth certificate

NoClass are totals where an occupation is given but could not be coded to social class (see text)

Table 3.7 Parameters of distributions of indoor gamma ray dose rates (nGy/hour)

	All records	Cases	Controls
Mean	94.8	94.9	94.7
SD	15.6	15.7	15.6
GM	93.4	93.5	93.4
GSD	1.2	1.2	1.2
Median	95.8	95.9	95.5
Decile			
1	74.7	74.9	74.7
2	80.8	80.8	80.8
3	85.8	85.8	85.8
4	90.6	90.6	90.4
5	95.8	95.9	95.5
6	100.9	100.9	100.7
7	105.0	105.1	105.0
8	108.0	108.1	108.0
9	114.5	114.5	114.5
10	159.7	159.7	159.7

Table 3.8 Parameters of distributions of indoor radon concentrations (Bq per metre cubed)

Data are presented for all records (cases and controls combined),
for all records with APGridsq radon estimates
for all cases and for all controls

	All records	APGridsq	Cases	Controls
Mean	21.3	21.7	21.3	21.3
SD	23.0	24.2	23.7	22.6
GM	16.4	16.5	16.4	16.4
GSD	2.0	2.0	2.0	2.0
Median	16.3	16.2	16.2	16.3
Decile				
1	7.3	7.2	7.3	7.3
2	9.3	9.2	9.3	9.3
3	11.1	11.1	11.1	11.2
4	13.6	13.5	13.6	13.6
5	16.3	16.2	16.2	16.3
6	18.9	19.1	18.8	18.9
7	22.6	22.8	22.6	22.7
8	27.7	28.0	27.6	27.8
9	38.1	38.9	38.0	38.1
10	692.1	692.1	692.1	692.1

Table 3.9 Trend analysis for childhood cancer grouping

Model includes cumulative radon exposure, cumulative gamma-ray exposure and quintiles of Carstairs index of deprivation

Exposure period taken as birth to diagnosis

				Relative Risk											
				Radon				Gamma				Quintiles of Carstairs Index			
ICCC3 codes	Diagnostic grouping	Number of Cases	Number of Controls	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 Leukaemia	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	11912	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's disease	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	Non-Hodgkin Lymphoma	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	Lymph. Leuk. + NHL	8250	10873	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 Leuk. + NHL	10041	13214	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/CNS (inc. Benign)	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	12610	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	Not Leukaemia	18389	24881	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	27447	36793	1.08	0.95	1.23	0.25	**1.03**	1.00	1.07	0.04	**0.98**	0.97	0.99	0.01

[a]RR for each 10^3 Bq/m^3 - years increase in cumulative radon exposure

[b]RR for each mGray increase in cumulative gamma-ray exposure

[c]RR for each quintile increase on the Carstairs Index of deprivation

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)

Table 3.10: Trend Analysis with Social class based on father's occupation as socio-economic status parameter

Analyses considering cumulative radon exposure, cumulative gamma-ray exposure and

Fathers Social Class as deduced from his occupation listed on the childs birth record

Exposure period taken as birth to diagnosis

				Relative risk Fathers Social Class deduced from occupation											
				Radon				Gamma				Occupational Social Class			
ICCC3 Codes	Diagnostic Grouping	Number of Cases	Number of Controls	RRa	95% CI		P	RRb	95% CI		P	RRc	95% CI		P
11	Lymphoid Leukaemia	6258	7861	1.20	0.91	1.60	0.20	1.08	1.00	1.17	0.06	**0.95**	0.92	0.97	<0.001
12	Acute Myeloid leukaemia	1110	1405	0.84	0.41	1.69	0.62	0.96	0.82	1.13	0.63	0.99	0.94	1.06	0.86
13-15	Other Leukaemia	401	495	0.88	0.34	2.29	0.79	1.22	0.91	1.65	0.19	0.98	0.89	1.08	0.71
11-15	Total Leukaemia	7769	9761	1.12	0.87	1.44	0.38	1.06	0.99	1.14	0.08	**0.96**	0.93	0.98	<0.001
21	Hodgkin's disease	798	1110	1.05	0.65	1.69	0.86	1.02	0.91	1.14	0.74	1.05	0.98	1.13	0.15
22	Non-Hodgkin Lymphoma	853	1072	1.19	0.63	2.24	0.59	1.03	0.88	1.22	0.71	0.97	0.91	1.04	0.42
21-25	Total Lymphona	1994	2660	1.09	0.76	1.55	0.65	1.00	0.91	1.09	0.94	1.02	0.98	1.07	0.39
11 ,22	Lymph. Leuk. + NHL	7111	8933	1.20	0.93	1.55	0.17	1.07	1.00	1.15	0.06	**0.95**	0.93	0.97	<0.001
11-15, 22	Total Leuk. + NHL	8622	10833	1.13	0.89	1.42	0.31	1.06	0.99	1.13	0.08	**0.96**	0.94	0.98	<0.001
31-36	Brain/CNS (inc. Benign)	5625	7317	1.15	0.87	1.52	0.33	1.04	0.98	1.11	0.22	**0.97**	0.94	0.99	0.01
41-122	Other malignant tumours	8053	10208	1.06	0.84	1.35	0.60	1.03	0.96	1.09	0.43	**0.98**	0.95	1.00	0.03
21-122	Not Leukaemia	15672	20185	1.09	0.93	1.28	0.27	1.02	0.98	1.07	0.23	**0.98**	0.96	0.99	0.01
11-122	Total Childhood Cancer	23441	29946	1.10	0.96	1.26	0.16	1.03	1.00	1.07	0.06	**0.97**	0.96	0.98	<0.001

[a]RR for each 10^3 Bq/m^3 - years increase in cumulative radon exposure

[b]RR for each mGy increase in cumulative gamma exposure

[c]RR for each decrease in occupational social class

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),

RRs in bold and double underlined are significantly different from 1 (P<0.001)

Table 3.11 Trend analysis using Carstairs scores rather than quintiles

Cumulative Radon exposure, cumulative Gamma-ray exposure and Carstairs deprivation scores

Exposure period taken as birth to diagnosis

				Relative risk							
				Radon				Gamma			
ICCC3 Codes	Diagnostic grouping	Number of Cases	Number of Controls	RR[a]	95% CI		P	RR[b]	95% CI		P
11	Lymphoid Leukaemia	7267	9571	1.24	0.94	1.64	0.13	**1.10**	1.02	1.18	0.02
12	Acute Myeloid leukaemia	1316	1737	0.71	0.37	1.39	0.32	1.04	0.89	1.21	0.61
13-15	Other Leukaemia	475	604	1.04	0.41	2.59	0.94	1.20	0.90	1.59	0.21
11-15	Total Leukaemia	9058	11912	1.12	0.88	1.43	0.35	**1.09**	1.02	1.16	0.01
21	Hodgkin's disease	939	1388	1.06	0.67	1.70	0.79	1.04	0.93	1.16	0.52
22	Non-Hodgkin Lymphoma	983	1302	1.24	0.67	3.31	0.50	1.04	0.90	1.22	0.57
21-25	Total Lymphoma	2319	3274	1.12	0.79	1.59	0.52	1.01	0.93	1.10	0.81
11 ,22	Lymph. Leuk. + NHL	8250	10873	1.24	0.96	1.59	0.10	**1.09**	1.01	1.16	0.02
11-15, 22	Total Leuk. + NHL	10041	13214	1.13	0.90	1.42	0.27	**1.08**	1.02	1.15	0.01
31-36	Brain/CNS (inc. Benign)	6585	8997	1.14	0.87	1.50	0.33	1.02	0.96	1.09	0.49
41-122	Other malignant tumours	9485	12610	1.00	0.80	1.24	0.98	1.02	0.96	1.08	0.60
21-122	Not Leukaemia	18389	24881	1.06	0.91	1.24	0.43	1.02	0.98	1.06	0.39
11-122	Total Childhood Cancer	27447	36793	1.08	0.95	1.23	0.24	**1.03**	1.00	1.07	0.04

[a]RR for each 10^3 Bq/m^3 - years increase in cumulative radon exposure

[b]RR for each mGy increase in cumulative gamma exposure

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)

Table 3.12 Trend Analysis with no allowance for socio-economic status

Analyses considering cumulative radon exposure and cumulative gamma-ray exposure

Exposure period taken as birth to diagnosis

				Relative risk No SES Variable included in analysis							
				Radon				Gamma			
ICCC3 Codes	Diagnostic grouping	Number of Cases	Number of Controls	RR[a]	95% CI		P	RR[b]	95% CI		P
11	Lymphoid Leukaemia	7267	9571	1.28	0.96	1.69	0.09	**1.09**	1.01	1.18	0.02
12	Acute Myeloid leukaemia	1316	1737	0.73	0.37	1.41	0.34	1.04	0.89	1.21	0.62
13-15	Other Leukaemia	475	604	0.92	0.37	2.30	0.86	1.20	0.91	1.59	0.20
11-15	Total Leukaemia	9058	11912	1.15	0.90	1.46	0.27	**1.09**	1.02	1.16	0.01
21	Hodgkin's disease	939	1388	1.05	0.66	1.67	0.84	1.04	0.93	1.16	0.50
22	Non-Hodgkin Lymphoma	983	1302	1.22	0.66	2.27	0.53	1.04	0.90	1.22	0.57
21-25	Total Lymphona	2319	3274	1.11	0.78	1.57	0.57	1.01	0.93	1.10	0.78
11 ,22	Lymph. Leuk. + NHL	8250	10873	1.27	0.98	1.63	0.07	**1.08**	1.01	1.16	0.02
11-15, 22	Total Leuk. + NHL	10041	13214	1.16	0.92	1.45	0.21	**1.08**	1.02	1.15	0.01
31-36	Brain/CNS (inc. Benign)	6585	8997	1.17	0.89	1.53	0.26	1.02	0.96	1.08	0.56
41-122	Other malignant tumours	9485	12610	1.00	0.81	1.24	1.00	1.01	0.96	1.07	0.61
21-122	Not Leukaemia	18389	24881	1.07	0.92	1.24	0.38	1.02	0.98	1.05	0.42
11-122	Total Childhood Cancer	27447	36793	1.09	0.96	1.24	0.18	1.03	1.00	1.07	0.06

[a]RR for each 10^3 Bq/m^3 - years increase in cumulative radon exposure

[b]RR for each mGy increase in cumulative gamma exposure

RRs in bold are significantly different from 1.00 (P<0.05),

Table 3.13 Trend analyses for Radon and Gamma rays as separate explanatory variables

Quintile of Carstairs index of deprivation with either cumulative radon exposure or cumulative gamma-ray exposure

Exposure period taken as birth to diagnosis

ICCC3 Codes	Diagnostic grouping	Number of Cases	Number of Controls	Relative risk Cumulative Radon exposure and ward quintiles				Relative risk Cumulative Gamma ray exposure and ward quintiles			
				RR[a]	95% CI		P	RR[b]	95% CI		P
11	Lymphoid Leukaemia	7267	9571	1.25	0.95	1.65	0.12	**1.10**	1.02	1.19	0.01
12	Acute Myeloid leukaemia	1316	1737	0.73	0.38	1.42	0.36	1.04	0.89	1.20	0.65
13-15	Other Leukaemia	475	604	1.07	0.43	2.65	0.89	1.19	0.90	1.57	0.23
11-15	Total Leukaemia	9058	11912	1.13	0.89	1.44	0.31	**1.09**	1.02	1.17	0.01
21	Hodgkin's disease	939	1388	1.07	0.67	1.71	0.79	1.04	0.93	1.16	0.53
22	Non-Hodgkin Lymphoma	983	1302	1.30	0.70	2.42	0.40	1.05	0.90	1.22	0.57
21-25	Total Lymphona	2319	3274	1.14	0.80	1.62	0.46	1.01	0.93	1.09	0.84
11 ,22	Lymph. Leuk. + NHL	8250	10873	1.25	0.97	1.61	0.08	**1.09**	1.02	1.17	0.01
11-15, 22	Total Leuk. + NHL	10041	13214	1.15	0.92	1.44	0.22	**1.08**	1.02	1.15	0.01
31-36	Brain/CNS (inc. Benign)	6585	8997	1.15	0.88	1.51	0.31	1.02	0.96	1.09	0.48
41-122	Other malignant tumours	9485	12610	0.99	0.80	1.23	0.96	1.02	0.96	1.08	0.57
21-122	Not Leukaemia	18389	24881	1.06	0.92	1.24	0.42	1.02	0.98	1.06	0.37
11-122	Total Childhood Cancer	27447	36793	1.08	0.95	1.23	0.22	**1.04**	1.00	1.07	0.04

[a]RR for each 10^3 Bq/m^3 - years increase in cumulative radon exposure

[b]RR for each mGy increase in cumulative gamma exposure

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)

Table 3.14 Test for trend as main analysis but restricted to case/control sets with GridSq-AP radon estimates

Cumulative radon exposure, cumulative gamma-ray exposure and quintiles of Carstairs index of deprivation

Exposure period taken as birth to diagnosis

ICCC3 Codes	Diagnostic grouping	Number of Cases	Number of Controls	Relative risk Radon				Relative risk Gamma			
				RR[a]	95% CI		P	RR[b]	95% CI		P
11	Lymphoid Leukaemia	6089	7895	1.19	0.89	1.59	0.25	**1.09**	1.00	1.19	0.05
12	Acute Myeloid leukaemia	1113	1440	0.61	0.30	1.25	0.18	1.09	0.92	1.29	0.32
13-15	Other Leukaemia	397	510	1.00	0.32	3.11	1.00	1.28	0.94	1.76	0.12
11-15	Total Leukaemia	7599	9845	1.07	0.82	1.38	0.35	**1.10**	1.02	1.18	0.02
21	Hodgkin's disease	804	1129	0.98	0.58	1.66	0.95	1.04	0.92	1.18	0.50
22	Non-Hodgkin Lymphoma	823	1065	1.21	0.63	2.33	0.56	1.07	0.91	1.27	0.41
21-25	Total Lymphona	1961	2690	1.07	0.73	1.56	0.73	1.01	0.92	1.10	0.83
11 ,22	Lymph. Leuk. + NHL	6912	8960	1.18	0.91	1.54	0.21	**1.08**	1.00	1.17	0.04
11-15, 22	Total Leuk. + NHL	8422	10910	1.08	0.85	1.37	0.53	**1.09**	1.02	1.17	0.01
31-36	Brain/CNS (inc. Benign)	5589	7501	1.20	0.90	1.61	0.21	0.99	0.93	1.06	0.75
41-122	Other malignant tumours	7872	10234	1.01	0.81	1.28	0.91	1.01	0.94	1.07	0.84
21-122	Not Leukaemia	15422	20425	1.08	0.91	1.27	0.38	1.00	0.96	1.04	0.96
11-122	Total Childhood Cancer	23021	30270	1.07	0.93	1.23	0.32	1.02	0.99	1.06	0.22

[a]RR for each 10^3 Bq/m^3 - years increase in cumulative radon exposure

[b]RR for each mGy increase in cumulative gamma exposure

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)

Table 3.15 Trend analyses using alternative estimate of radon concentration

Cumulative radon exposure, cumulative gamma-ray exposure and quintiles of Carstairs index of deprivation

Radon exposure estimated as mean for the County District of birth

Exposure period taken as birth to diagnosis

				Radon				Gamma			
ICCC3	Diagnostic grouping	Number of Cases	Number of Controls	RR[a]	95% CI		P	RR[b]	95% CI		P
11	Lymphoid Leukaemia	7267	9571	0.93	0.82	1.06	0.28	**1.10**	1.02	1.19	0.01
12	Acute Myeloid Leukaemia	1316	1737	1.00	0.71	1.40	0.98	1.04	0.89	1.20	0.65
13-15	Other Leukaemia	475	604	0.66	0.15	2.93	0.59	1.19	0.89	1.57	0.24
11-15	Total Leukaemia	9058	11912	0.94	0.83	1.05	0.28	**1.09**	1.02	1.17	0.01
21	Hodgkin's disease	939	1388	0.90	0.61	1.34	0.60	1.04	0.93	1.16	0.52
22	Non-Hodgkin Lymphoma	983	1302	1.01	0.73	1.39	0.96	1.05	0.90	1.22	0.56
21-25	Total Lymphoma	2319	3274	0.98	0.77	1.24	0.85	1.01	0.93	1.09	0.84
11, 22	Lymph. Leuk. + NHL	8250	10873	0.94	0.84	1.06	0.31	**1.09**	1.02	1.17	0.01
11-15, 22	Total Leuk. + NHL	10041	13214	0.94	0.85	1.05	0.30	**1.09**	1.02	1.15	0.01
31-36	Brain/CNS (inc. Benign)	6585	8997	0.96	0.87	1.06	0.42	1.02	0.96	1.09	0.46
41-122	Other malignant tumours	9485	12610	1.00	0.92	1.09	0.96	1.02	0.96	1.08	0.57
21-122	Not Leukaemia	18389	24881	0.98	0.92	1.04	0.58	1.02	0.98	1.06	0.36
11-122	Total Childhood Cancer	27447	36793	0.97	0.92	1.03	0.31	**1.04**	1.00	1.07	0.03

[a]RR for each 103 Bq/m3 - years increase in cumulative radon exposure

[b]RR for each mGy increase in cumulative gamma exposure

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)

Table 3.16 Trend analysis considering radon concentrations and gamma ray dose rates

Radon concentration, daily gamma-ray dose rate and Quintile of Carstairs index of deprivation

Exposure period taken as birth to diagnosis

ICCC3 Codes	Diagnostic grouping	Number of Cases	Number of Controls	Relative Risk							
				Radon				Gamma			
				RR[a]	95% CI		p	RR[b]	95% CI		p
11	Lymphoid Leukaemia	7267	9571	1.05	0.88	1.25	0.60	1.14	0.97	1.34	0.12
12	Acute Myeloid leukaemia	1316	1737	0.68	0.44	1.07	0.10	1.07	0.73	1.57	0.74
13-15	Other Leukaemia	475	604	0.93	0.52	1.66	0.81	1.59	0.86	2.94	0.14
11-15	Total Leukaemia	9058	11912	0.98	0.83	1.14	0.76	1.15	0.99	1.33	0.06
21	Hodgkin's disease	939	1388	1.10	0.63	1.91	0.73	1.23	0.78	1.92	0.37
22	Non-Hodgkin Lymphoma	983	1302	1.58	0.88	2.82	0.13	1.16	0.72	1.88	0.54
21-25	Total Lymphoma	2319	3274	1.31	0.92	1.86	0.13	1.01	0.76	1.35	0.93
11 ,22	Lymph. Leuk. + NHL	8250	10873	1.08	0.92	1.28	0.35	1.14	0.98	1.33	0.10
11-15, 22	Total Leuk. + NHL	10041	13214	1.01	0.87	1.17	0.92	1.15	1.00	1.32	0.05
31-36	Brain/CNS (inc. Benign)	6585	8997	1.14	0.94	1.37	0.18	1.08	0.91	1.28	0.38
41-122	Other malignant tumours	9485	12610	0.95	0.81	1.11	0.49	0.92	0.80	1.06	0.25
21-122	Not Leukaemia	18389	24881	1.05	0.94	1.17	0.42	0.98	0.89	1.09	0.77
11-122	Total Childhood Cancer	27447	36793	1.02	0.93	1.12	0.64	1.04	0.95	1.13	0.41

[a]RR for each 10^2 Bq/m^3 increase in radon concentration

[b]RR for each µGy per day increase in gamma ray dose rate

Table 3.17 Trend analysis for cumulative RBM dose from radon and gamma rays separately and combined

Cumulative RBM dose (mSv) and quintiles of Carstairs index of deprivation

Exposure period taken as birth to diagnosis

	Relative risk per mSv RBM dose for model containing gamma rays and radon separately								Relative risk per mSv for model including combined RBM dose 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	**<u>1.09</u>**	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 Leukaemia	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	**<u>1.12</u>**	1.03	1.22	0.01	**1.07**	1.01	1.13	0.02

[a]RR for each mSv increase in RBM radon dose

[b]RR for each mSv increase in RBM gamma ray dose

[c]RR for each mSv increase in RBM natural radiation dose from gamma rays and radon combined

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)

Table 3.18 Trend analyses for Males and Females separately

Cumulative Radon exposure, Cumulative Gamma ray exposure and quintiles of Carstairs index of deprivation

Exposure period taken as birth to diagnosis

		Relative risk for Males										Relative risk for Females							
				Radon				Gamma						Radon				Gamma			
ICCC3	Diagnostic grouping	Number of cases	Number of controls	RR[a]	95% CI		P	RR[b]	95% CI		P	Number of cases	Number of controls	RR[a]	95% CI		P	RR[b]	95% CI		P
11	Lymphoid Leukaemia	4085	5402	1.24	0.85	1.79	0.26	**1.11**	1.01	1.23	0.03	3182	4169	1.25	0.82	1.91	0.30	1.08	0.96	1.22	0.22
12	Acute Myeloid leukaemia	704	924	0.65	0.25	1.66	0.37	1.02	0.81	1.27	0.90	612	813	0.82	0.32	2.08	0.67	1.07	0.87	1.32	0.50
13-15	Other Leukaemia	265	335	0.30	0.05	1.78	0.18	1.14	0.76	1.72	0.52	210	269	8.53	0.81	89.31	0.07	1.17	0.77	1.77	0.47
11-15	Total Leukaemia	5054	6661	1.03	0.74	1.43	0.85	**1.10**	1.01	1.20	0.04	4004	5251	1.25	0.86	1.82	0.24	1.08	0.98	1.20	0.12
21	Hodgkin's disease	616	900	0.94	0.49	1.82	0.86	1.04	0.90	1.19	0.64	323	488	1.20	0.62	2.34	0.59	1.02	0.85	1.21	0.85
22	Non-Hodgkin Lymphoma	663	866	1.51	0.70	3.24	0.29	1.10	0.91	1.32	0.31	320	436	0.92	0.29	2.88	0.88	0.92	0.70	1.21	0.55
21-25	Total Lymphoma	1591	2227	1.08	0.69	1.71	0.73	1.02	0.92	1.12	0.74	728	1047	1.22	0.71	2.12	0.47	0.98	0.85	1.14	0.83
11 ,22	Lymph. Leuk. + NHL	4748	6268	1.27	0.91	1.78	0.16	**1.11**	1.02	1.21	0.02	3502	4605	1.20	0.81	1.78	0.36	1.05	0.94	1.17	0.38
11-15, 22	Total Leuk. + NHL	5717	7527	1.09	0.81	1.47	0.58	**1.10**	1.01	1.19	0.02	4324	5687	1.21	0.85	1.72	0.28	1.06	0.97	1.17	0.21
31-36	Brain/CNS (inc. Benign)	3540	4875	1.01	0.70	1.46	0.95	1.03	0.95	1.12	0.46	3045	4122	1.34	0.89	2.01	0.16	1.01	0.92	1.10	0.85
41-122	Other malignant tumours	4920	6495	1.02	0.74	1.42	0.89	0.99	0.91	1.08	0.88	4565	6115	0.97	0.72	1.29	0.83	1.04	0.96	1.13	0.35
21-122	Not Leukaemia	10051	13597	1.03	0.83	1.28	0.79	1.01	0.96	1.07	0.61	8338	11284	1.10	0.89	1.36	0.39	1.02	0.97	1.08	0.46
11-122	Total Childhood Cancer	15105	20258	1.03	0.86	1.23	0.75	1.03	0.99	1.08	0.13	12342	16535	1.14	0.94	1.37	0.18	1.04	0.99	1.09	0.16

[a]RR for each 10^3 Bq/m^3 - years increase in cumulative radon exposure

[b]RR for each mGy increase in cumulative gamma exposure

RRs in bold are significantly different from 1.00 (P<0.05)

Table 3.19: Trend analysis for age groups less than 1Y and 1-4 Y

Cumulative radon exposure, cumulative gamma-ray exposure and quintiles of Carstairs index of deprivation

Exposure period taken as birth to diagnosis

				Relative risks at ages less than 1 Y										Relative Risks at ages 1-4 Y							
				Radon				Gamma						Radon				Gamma			
ICCC3 Codes	Diagnostic grouping	Number of cases	Number of controls	RR[c]	95% CI		P	RR[d]	95% CI		P	Number of cases	Number of controls	RR[a]	95% CI		P	RR[b]	95% CI		P
11	Lymphoid Leukaemia	337	428	1.00	0.98	1.03	0.65	1.02	0.99	1.06	0.12	4182	5339	0.98	0.91	1.06	0.68	1.00	0.98	1.02	0.82
12	Acute Myeloid leukaemia	237	306	0.99	0.97	1.01	0.51	1.01	0.97	1.05	0.56	521	649	1.03	0.77	1.38	0.83	0.99	0.94	1.05	0.79
13-15	Other Leukaemia	115	148	0.99	0.97	1.02	0.46	1.00	0.93	1.07	0.89	190	226	0.96	0.53	1.74	0.89	1.03	0.96	1.11	0.43
11-15	Total Leukaemia	689	882	1.00	0.99	1.01	0.42	1.02	0.99	1.04	0.16	4893	6214	0.98	0.91	1.06	0.68	1.00	0.98	1.02	0.93
21	Hodgkin's disease											82	113	1.06	0.53	2.13	0.87	1.11	0.99	1.25	0.07
22	Non-Hodgkin Lymphoma	14	18	1.25	1.01	1.53	0.04	1.07	0.94	1.21	0.31	273	333	1.26	0.84	1.89	0.26	1.00	0.92	1.07	0.90
21-25	Total Lymphoma	23	29	1.28	1.03	1.59	0.03	1.05	0.95	1.15	0.37	468	603	1.18	0.90	1.54	0.24	1.00	0.95	1.05	1.00
11 ,22	Lymph. Leuk. + NHL	351	446	1.01	0.99	1.03	0.44	1.03	1.00	1.06	0.05	4455	5672	0.99	0.92	1.07	0.84	1.00	0.98	1.01	0.80
11-15, 22	Total Leuk. + NHL	703	900	1.00	0.99	1.01	0.52	1.02	1.00	1.04	0.08	5166	6547	0.99	0.92	1.07	0.84	1.00	0.98	1.01	0.90
31-36	Brain/CNS (inc. Benign)	584	743	1.00	0.99	1.01	0.90	1.02	1.00	1.04	0.12	2351	3097	1.05	0.94	1.17	0.38	1.01	0.99	1.04	0.26
41-122	Other malignant tumours	2015	2602	1.00	0.99	1.01	0.75	1.00	0.99	1.01	0.92	4101	5186	0.97	0.89	1.05	0.44	0.99	0.97	1.01	0.29
21-122	Not Leukaemia	2622	3374	1.00	0.99	1.01	0.96	1.01	1.00	1.02	0.28	6920	8886	1.01	0.95	1.07	0.86	1.00	0.98	1.01	0.92
11-122	Total Childhood Cancer	3311	4256	1.00	0.99	1.00	0.71	1.01	1.00	1.02	0.11	11813	15100	1.00	0.95	1.04	0.89	1.00	0.99	1.01	0.89

[a]RR for each Bq/m3 - years increase in cumulative radon exposure

bRR for each 10nGy increase in cumulative gamma exposure

[c]RR for each 100 Bq/m3 - years increase in cumulative radon exposure

[d]RR for each 100nGy increase in cumulative gamma exposure

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)

Table 3.20 Trend analyses for age groups 5-9 and 10-14

Cumulative radon exposure, cumulative gamma-ray exposure and quintiles of Carstairs index of deprivation

Exposure period taken as birth to diagnosis

				Relative risks at ages 5-9										Relative risks at ages 10-14							
		Number of cases	Number of controls	Radon				Gamma				Number of cases	Number of controls	Radon				Gamma			
ICCC3	Diagnostic grouping			RR[e]	95% CI		P	RR[f]	95% CI		P			RR[e]	95% CI		P	RR[f]	95% CI		P
11	Lymphoid Leukaemia	1904	2561	1.41	0.92	2.17	0.12	**1.20**	1.05	1.37	0.01	844	1243	1.25	0.80	1.96	0.32	1.09	0.97	1.21	0.13
12	Acute Myeloid leukaemia	288	393	**0.13**	0.02	0.73	0.02	0.99	0.71	1.37	0.94	270	389	1.12	0.50	2.51	0.79	1.05	0.87	1.26	0.64
13-15	Other Leukaemia	91	117	1.15	0.28	4.74	0.85	1.17	0.70	1.96	0.54	79	113	1.03	0.29	3.69	0.96	1.14	0.79	1.66	0.48
11-15	Total Leukaemia	2283	3071	1.14	0.79	1.65	0.47	**1.16**	1.03	1.31	0.02	1193	1745	1.18	0.82	1.71	0.37	1.08	0.99	1.19	0.08
21	Hodgkin's disease	275	385	2.76	0.46	16.50	0.27	0.91	0.65	1.26	0.56	582	890	0.97	0.59	1.59	0.90	1.05	0.94	1.19	0.38
22	Non-Hodgkin Lymphoma	371	476	2.20	0.79	6.14	0.13	1.15	0.88	1.49	0.30	325	475	0.69	0.25	1.90	0.48	1.02	0.84	1.24	0.84
21-25	Total Lymphoma	803	1096	2.19	0.97	4.96	0.06	1.02	0.85	1.22	0.83	1025	1546	0.90	0.59	1.37	0.62	1.01	0.92	1.11	0.87
11 ,22	Lymph. Leuk. + NHL	2275	3037	**1.52**	1.02	2.28	0.04	**1.19**	1.05	1.34	0.01	1169	1718	1.12	0.76	1.66	0.56	1.06	0.97	1.17	0.22
11-15, 22	Total Leuk. + NHL	2654	3547	1.25	0.89	1.76	0.20	**1.16**	1.04	1.29	0.01	1519	2221	1.10	0.79	1.54	0.58	1.07	0.98	1.16	0.12
31-36	Brain/CNS (inc. Benign)	2231	3033	1.03	0.70	1.59	0.89	0.97	0.88	1.08	0.60	1419	2124	1.17	0.81	1.70	0.41	1.04	0.96	1.13	0.34
41-122	Other malignant tumours	1638	2210	1.05	0.74	1.49	0.78	1.02	0.90	1.15	0.77	1731	2612	0.97	0.72	1.30	0.81	1.03	0.96	1.10	0.39
21-122	Not Leukaemia	4672	6339	1.14	0.89	1.47	0.31	0.99	0.93	1.07	0.88	4175	6282	1.00	0.82	1.22	0.99	1.03	0.98	1.08	0.24
11-122	Total Childhood Cancer	6955	9410	1.14	0.92	1.40	0.23	1.04	0.97	1.10	0.26	5368	8027	1.04	0.87	1.24	0.65	1.04	1.00	1.08	0.06

[e]OR for each 103 Bq/m^3 - years increase in cumulative radon exposure

[f]OR for each mGray increase in cumulative

ORs in bold are significantly different from 1.00 (P<0.05); ORs in bold and underlined are significantly different from 1 (P<0.01) gamma exposure

Table 3.21 Trend analysis for leukaemia and lymphoid leukaemia by single year of age at diagnosis

Cumulative radon exposure, cumulative gamma-ray exposure and quintiles of Carstairs index of deprivation

Exposure period taken as birth to diagnosis

			Relative risk Total leukaemia										Relative risk Lymphoid leukaemia							
			Radon				Gamma				Number of	Number of	Radon				Gamma			
Age at diagnosis	Number of cases	Number of controls	RR[a]	95% CI		P	RR[b]	95% CI		P	cases	controls	RR[a]	95% CI		P	RR[b]	95% CI		P
0-14	9058	11912	1.12	0.88	1.43	0.35	**1.09**	1.02	1.17	0.01	7267	9571	1.24	0.94	1.63	0.13	1.10	1.02	1.19	0.01
0	689	882	1.00	0.99	1.01	0.42	4.87	0.54	44.24	0.16	337	428	1.00	0.98	1.03	0.65	11.68	0.53	255.49	0.12
1	984	1224	**0.67**	0.45	0.99	0.05	1.51	0.70	3.24	0.29	670	840	0.65	0.41	1.03	0.06	1.62	0.64	4.07	0.31
2	1464	1865	1.00	0.87	1.14	0.99	1.15	0.78	1.69	0.47	1305	1668	1.00	0.86	1.15	0.96	1.08	0.72	1.62	0.72
3	1407	1799	0.93	0.81	1.07	0.32	1.11	0.83	1.48	0.49	1273	1636	0.95	0.82	1.09	0.46	1.11	0.82	1.50	0.50
4	1038	1326	1.03	0.90	1.17	0.68	0.81	0.63	1.04	0.10	934	1195	1.02	0.89	1.16	0.81	0.78	0.60	1.03	0.08
5	721	963	2.93	0.78	10.93	0.11	1.14	0.87	1.48	0.35	641	860	**5.40**	1.05	27.74	0.04	1.09	0.82	1.44	0.56
6	524	687	0.84	0.31	2.29	0.74	1.20	0.90	1.60	0.21	448	587	0.91	0.33	2.57	0.86	1.17	0.85	1.60	0.33
7	421	560	1.64	0.60	4.52	0.34	1.09	0.82	1.45	0.54	340	450	4.46	0.89	22.32	0.07	1.14	0.82	1.58	0.45
8	320	442	0.88	0.26	3.03	0.84	1.21	0.90	1.62	0.20	255	360	1.54	0.27	8.64	0.62	1.23	0.90	1.69	0.19
9	297	419	1.05	0.62	1.80	0.85	1.20	0.94	1.53	0.15	220	304	1.16	0.67	2.00	0.60	**1.39**	1.02	1.90	0.04
10	269	377	0.58	0.13	2.51	0.47	1.31	0.99	1.74	0.06	206	294	0.42	0.08	2.20	0.31	1.26	0.91	1.75	0.16
11	247	352	0.92	0.31	2.71	0.89	1.08	0.88	1.32	0.47	164	234	1.03	0.22	4.78	0.97	1.18	0.93	1.50	0.17
12	238	340	1.68	0.56	5.04	0.36	1.05	0.84	1.30	0.68	166	241	1.13	0.34	3.75	0.84	1.07	0.80	1.42	0.67
13	224	346	0.92	0.50	1.69	0.78	1.00	0.83	1.21	0.98	155	235	1.13	0.55	2.32	0.75	1.02	0.81	1.29	0.84
14	215	325	1.25	0.62	2.51	0.53	1.11	0.91	1.34	0.30	153	237	1.41	0.58	3.41	0.45	1.04	0.84	1.28	0.75

[a]RR for each Bq/m^3 - years increase in cumulative radon exposure for cases diagnosed at age 0

RR for each 100 Bq/m^3 - years increase in cumulative radon exposure for cases diagnosed at ages 1-4

RR for each 10^3 Bq/m^3 - years increase in cumulative radon exposure for cases diagnosed at ages 5-14

[b]RR for each mGy increase in cumulative gamma exposure

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)

Table 3.22 Trend analysis with different assumptions about latent period (0 and 9 months)

Cumulative radon exposure, cumulative gamma-ray exposure and quintiles of Carstairs index of deprivation

ICCC3		Number of Cases	Number of Controls	Relative risk							
				Radon				Gamma			
				RR[a]	95% CI		P	RR[b]	95% CI		P
Exposure period: Conception to diagnosis											
11	Lymphoid Leukaemia	7267	9571	1.20	0.93	1.55	0.15	**1.09**	1.02	1.16	0.02
12	Acute Myeloid Leukaemia	1316	1737	0.72	0.39	1.33	0.29	1.04	0.90	1.20	0.59
13-15	Other Leukaemia	475	604	1.02	0.44	2.38	0.96	1.18	0.91	1.53	0.20
11-15	Total Leukaemia	9058	11912	1.10	0.88	1.37	0.41	**1.08**	1.02	1.15	0.01
21	Hodgkin's disease	939	1388	1.06	0.68	1.65	0.78	1.03	0.93	1.15	0.52
22	Non-Hodgkin Lymphoma	983	1302	1.29	0.72	2.29	0.39	1.04	0.90	1.20	0.60
21-25	Total Lymphoma	2319	3274	1.14	0.82	1.58	0.43	1.01	0.93	1.09	0.87
11, 22	Lymph. Leuk. + NHL	8250	10873	1.21	0.96	1.52	0.11	**1.08**	1.01	1.15	0.02
11-15, 22	Total Leuk. + NHL	10041	13214	1.11	0.91	1.37	0.30	**1.08**	1.02	1.14	0.01
31-36	Brain/CNS (inc. Benign)	6585	8997	1.14	0.89	1.46	0.29	1.02	0.96	1.08	0.47
41-122	Other malignant tumours	9485	12610	0.99	0.81	1.21	0.90	1.01	0.96	1.07	0.62
21-122	Not Leukaemia	18389	24881	1.06	0.92	1.22	0.42	1.02	0.98	1.05	0.40
11-122	Total Childhood Cancer	27447	36793	1.07	0.95	1.20	0.26	**1.03**	1.00	1.06	0.04
Exposure period: Birth to Diagnosis, taken as conception to diagnosis less 9 months											
11	Lymphoid Leukaemia	7267	9571	1.24	0.94	1.64	0.13	**1.10**	1.02	1.19	0.01
12	Acute Myeloid Leukaemia	1316	1737	0.72	0.37	1.40	0.34	1.04	0.89	1.21	0.60
13-15	Other Leukaemia	475	604	1.04	0.41	2.61	0.94	1.19	0.90	1.57	0.23
11-15	Total Leukaemia	9058	11912	1.12	0.88	1.43	0.35	**1.09**	1.02	1.17	0.01
21	Hodgkin's disease	939	1388	1.07	0.67	1.70	0.79	1.04	0.93	1.16	0.53
22	Non-Hodgkin Lymphoma	983	1302	1.29	0.69	2.39	0.43	1.04	0.89	1.21	0.61
21-25	Total Lymphoma	2319	3274	1.14	0.80	1.62	0.47	1.01	0.93	1.09	0.86
11, 22	Lymph. Leuk. + NHL	8250	10873	1.24	0.96	1.60	0.10	**1.09**	1.02	1.16	0.02
11-15, 22	Total Leuk. + NHL	10041	13214	1.14	0.91	1.43	0.27	**1.08**	1.02	1.15	0.01
31-36	Brain/CNS (inc. Benign)	6585	8997	1.15	0.88	1.50	0.32	1.02	0.96	1.09	0.49

				Relative risk							
				Radon				Gamma			
ICCC3		Number of Cases	Number of Controls	RR[a]	95% CI		P	RR[b]	95% CI		P
41-122	Other malignant tumours	9485	12610	0.99	0.80	1.23	0.95	1.02	0.96	1.08	0.57
21-122	Not Leukaemia	18389	24881	1.06	0.91	1.24	0.43	1.02	0.98	1.06	0.38
11-122	Total Childhood Cancer	27447	36793	1.08	0.95	1.23	0.25	**1.03**	1.00	1.07	0.04

aRR for each 103 Bq/m3 - years increase in cumulative radon exposure

bRR for each mGy increase in cumulative gamma exposure

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)

Table 3.23 Trend Analysis with different assumptions about latent period (12 and 24 months)

Cumulative radon exposure, cumulative gamma-ray exposure and quintiles of Carstairs index of deprivation

				Relative risk							
				Radon				Gamma			
ICCC3		Number of Cases	Number of Controls	RR[a]	95% CI		P	RR[b]	95% CI		P
Exposure period: Conception to diagnosis less 1 year											
11	Lymphoid Leukaemia	7184	9470	1.25	0.94	1.67	0.13	1.10	1.02	1.19	0.01
12	Acute Myeloid Leukaemia	1232	1636	0.72	0.36	1.43	0.35	1.04	0.89	1.22	0.59
13-15	Other Leukaemia	423	543	1.03	0.40	2.67	0.95	1.20	0.90	1.60	0.22
11-15	Total Leukaemia	8839	11649	1.13	0.88	1.45	0.34	1.10	1.02	1.17	0.01
21	Hodgkin's disease	939	1388	1.07	0.66	1.72	0.79	1.04	0.93	1.16	0.54
22	Non-Hodgkin Lymphoma	982	1301	1.28	0.68	2.43	0.44	1.04	0.89	1.22	0.61
21-25	Total Lymphoma	2312	3267	1.14	0.79	1.63	0.48	1.01	0.93	1.10	0.86
11, 22	Lymph. Leuk. + NHL	8166	10771	1.25	0.96	1.62	0.10	1.09	1.02	1.17	0.02
11-15, 22	Total Leuk. + NHL	9821	12950	1.14	0.91	1.44	0.26	1.09	1.02	1.16	0.01
31-36	Brain/CNS (inc. Benign)	6437	8811	1.14	0.87	1.51	0.34	1.02	0.96	1.09	0.51
41-122	Other malignant tumours	8777	11693	1.00	0.80	1.24	0.98	1.02	0.96	1.08	0.54
21-122	Not Leukaemia	17526	23771	1.06	0.91	1.24	0.43	1.02	0.98	1.06	0.37
11-122	Total Childhood Cancer	26365	35420	1.08	0.95	1.24	0.24	1.04	1.00	1.07	0.04
Exposure period: Conception to diagnosis less 2 years											
11	Lymphoid Leukaemia	6807	8987	1.32	0.95	1.85	0.10	**1.12**	1.02	1.23	0.01
12	Acute Myeloid Leukaemia	1012	1348	0.73	0.34	1.56	0.41	1.05	0.88	1.25	0.57
13-15	Other Leukaemia	340	433	1.03	0.35	3.02	0.95	1.19	0.86	1.65	0.30
11-15	Total Leukaemia	8159	10768	1.17	0.88	1.56	0.28	**1.11**	1.03	1.20	0.01
21	Hodgkin's disease	938	1386	1.07	0.64	1.80	0.80	1.04	0.92	1.17	0.56
22	Non-Hodgkin Lymphoma	962	1276	1.27	0.62	2.58	0.51	1.04	0.88	1.24	0.63
21-25	Total Lymphoma	2287	3234	1.13	0.76	1.68	0.54	1.01	0.92	1.10	0.86
11, 22	Lymph. Leuk. + NHL	7769	10263	1.30	0.96	1.76	0.09	**1.10**	1.02	1.20	0.02
11-15, 22	Total Leuk. + NHL	9121	12044	1.18	0.90	1.53	0.23	**1.10**	1.02	1.18	0.01
31-36	Brain/CNS (inc. Benign)	5852	8069	1.15	0.84	1.57	0.40	1.02	0.95	1.10	0.53

				Relative risk							
				Radon				Gamma			
ICCC3		Number of Cases	Number of Controls	RR[a]	95% CI		P	RR[b]	95% CI		P
41-122	Other malignant tumours	7037	9491	1.00	0.78	1.29	0.97	1.03	0.96	1.10	0.45
21-122	Not Leukaemia	15176	20794	1.07	0.90	1.27	0.46	1.02	0.98	1.07	0.34
11-122	Total Childhood Cancer	23335	31562	1.09	0.94	1.27	0.23	**1.04**	1.00	1.08	0.03

[a]RR for each 10^3 Bq/m^3 - years increase in cumulative radon exposure

[b]RR for each mGy increase in cumulative gamma exposure

RRs in bold are significantly different from 1.00 (P<0.05), RRs in bold and underlined significantly different from 1.00 (P<0.01)

Table 3.24: Assessment of Heterogeneity among RRs for Sex, Diagnosis Age Group and Age at Diagnosis by Individual Year

		Radon						Gamma					
		Sex		Grouped age at diagnosis		Single year of age at diagnosis		Sex		Grouped age at diagnosis		Single year of age at diagnosis	
ICCC3		chi2 (1 DF)	p	chi2 (3 DF)	p	chi2 (14 DF)	p	chi2 (1 DF)	p	chi2 (3 DF)	p	chi2 (14 DF)	p
11	Lymphoid Leukaemia	0.01	0.94	1.54	0.67	14.03	0.45	0.16	0.69	5.76	0.12	13.98	0.45
12	Acute Myeloid leukaemia	0.12	0.73	5.08	0.17	16.28	0.30	0.14	0.71	0.58	0.90	5.29	0.98
13-15	Other Leukaemia	**5.63**	0.02	1.14	0.77	8.52	0.86	0.04	0.84	0.46	0.93	16.87	0.26
11-15	Total Leukaemia	0.63	0.43	0.99	0.80	11.25	0.67	0.03	0.86	4.19	0.24	11.96	0.61
21	Hodgkin's disease	0.16	0.69	1.00	0.61	8.38	0.82	0.01	0.93	3.03	0.22	18.82	0.13
22	Non-Hodgkin Lymphoma	0.51	0.47	**8.35**	0.04	16.78	0.27	1.28	0.26	2.87	0.41	17.34	0.24
21-25	Total Lymphoma	0.12	0.73	**9.14**	0.03	17.03	0.25	0.07	0.80	1.56	0.67	17.26	0.24
11 ,22	Lymph. Leuk. + NHL	0.04	0.85	2.92	0.40	17.09	0.25	0.65	0.42	7.66	0.05	18.59	0.18
11-15, 22	Total Leuk. + NHL	0.24	0.63	0.77	0.86	12.63	0.56	0.29	0.59	5.61	0.13	16.96	0.26
31-36	Brain/CNS (inc. Benign)	1.21	0.27	0.81	0.85	7.69	0.90	0.15	0.70	4.73	0.19	16.16	0.30
41-122	Other malignant tumours	0.04	0.84	0.86	0.83	11.93	0.61	0.52	0.47	1.57	0.67	**25.92**	0.03
21-122	Not Leukaemia	0.26	0.61	0.62	0.89	11.76	0.63	0.02	0.89	1.73	0.63	7.92	0.89
11-122	Total Childhood Cancer	0.69	0.41	0.59	0.90	11.55	0.64	0.00	0.98	2.97	0.40	11.53	0.64

Results in bold are significant at the 5% level

Table 4.1 Main Trend Analysis

Cumulative radon exposure, cumulative gamma-ray exposure and quintiles of Carstairs index of deprivation

Exposure period taken as birth to diagnosis

				Relative risk							
				Radon				Gamma			
ICCC3 Codes	Diagnostic grouping	Number of Cases	Number of Controls	RR[a]	95% CI		p	RR[b]	95% CI		p
11	Lymphoid Leukaemia	7267	9571	1.24	0.94	1.64	0.13	**1.10**	1.02	1.19	0.01
12	Acute Myeloid leukaemia	1316	1737	0.72	0.37	1.40	0.34	1.04	0.89	1.21	0.60
13-15	Other Leukaemia	475	604	1.04	0.41	2.61	0.94	1.19	0.90	1.57	0.23
11-15	Total Leukaemia	9058	11912	1.12	0.88	1.43	0.35	**1.09**	1.02	1.17	0.01
21	Hodgkin's disease	939	1388	1.07	0.67	1.70	0.79	1.04	0.93	1.16	0.53
22	Non-Hodgkin Lymphoma	983	1302	1.29	0.69	2.39	0.43	1.04	0.89	1.21	0.61
21-25	Total Lymphoma	2319	3274	1.14	0.80	1.62	0.47	1.01	0.93	1.09	0.86
11 ,22	Lymph. Leuk. + NHL	8250	10873	1.24	0.96	1.60	0.10	**1.09**	1.02	1.16	0.02
11-15, 22	Total Leuk. + NHL	10041	13214	1.14	0.91	1.43	0.27	**1.08**	1.02	1.15	0.01
31-36	Brain/CNS (inc. Benign)	6585	8997	1.15	0.88	1.50	0.32	1.02	0.96	1.09	0.49
41-122	Other malignant tumours	9485	12610	0.99	0.80	1.23	0.95	1.02	0.96	1.08	0.57
21-122	Not Leukaemia	18389	24881	1.06	0.91	1.24	0.43	1.02	0.98	1.06	0.38
11-122	Total Childhood Cancer	27447	36793	1.08	0.95	1.23	0.25	**1.03**	1.00	1.07	0.04

[a]RR for each 10^3 Bq/m^3 - years increase in cumulative radon exposure

[b]RR for each mGy increase in cumulative gamma exposure

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)

Table 4.2 Odds ratios for Gamma rays using different measures of socioeconomic status

Analyses considering cumulative radon exposure, cumulative gamma-ray exposure and

a) Carstairs quintiles - Main analysis (27447 cases)

b) Carstairs scores rather than quintiles (27447 cases)

c) Fathers Social Class as deduced from his occupation listed on the childs birth certificate (23441 cases)

d) SES not included in the model (27447 cases)

Exposure period taken as birth to diagnosis

		Main Analysis (Carstairs Quintiles)				Carstairs scores rather than Quintiles				Fathers Social Class deduced from occupation				No allowance for SES			
ICCC3 Codes		OR[b]	95% CI		p	OR[b]	95% CI		P	OR[b]	95% CI		P	OR[b]	95% CI		P
11	Lymphoid Leukaemia	**1.10**	1.02	1.19	0.01	**1.13**	1.02	1.24	0.02	1.08	1.00	1.17	0.06	**1.09**	1.01	1.18	0.02
12	Acute Myeloid leukaemia	1.04	0.89	1.21	0.60	1.05	0.87	1.28	0.61	0.96	0.82	1.13	0.63	1.04	0.89	1.21	0.62
13-15	Other Leukaemia	1.19	0.90	1.57	0.23	1.26	0.88	1.80	0.21	1.22	0.91	1.65	0.19	1.20	0.91	1.59	0.20
11-15	Total Leukaemia	**1.09**	1.02	1.17	0.01	**1.12**	1.03	1.21	0.01	1.06	0.99	1.14	0.08	**1.09**	1.02	1.16	0.01
21	Hodgkin's disease	1.04	0.93	1.16	0.53	1.05	0.91	1.20	0.52	1.02	0.91	1.14	0.74	1.04	0.93	1.16	0.50
22	Non-Hodgkin Lymphoma	1.04	0.89	1.21	0.61	1.06	0.87	1.28	0.57	1.03	0.88	1.22	0.71	1.04	0.90	1.22	0.57
21-25	Total Lymphona	1.01	0.93	1.09	0.86	1.01	0.91	1.12	0.81	1.00	0.91	1.09	0.94	1.01	0.93	1.10	0.78
11 ,22	Lymph. Leuk. + NHL	**1.09**	1.02	1.16	0.02	**1.11**	1.02	1.21	0.02	1.07	1.00	1.15	0.06	**1.08**	1.01	1.16	0.02
11-15, 22	Total Leuk. + NHL	**1.08**	1.02	1.15	0.01	**1.11**	1.02	1.19	0.01	1.06	0.99	1.13	0.08	**1.08**	1.02	1.15	0.01
31-36	Brain/CNS (inc. Benign)	1.02	0.96	1.09	0.49	1.03	0.95	1.11	0.49	1.04	0.98	1.11	0.22	1.02	0.96	1.08	0.56
41-122	Other malignant tumours	1.02	0.96	1.08	0.57	1.02	0.95	1.10	0.60	1.03	0.96	1.09	0.43	1.01	0.96	1.07	0.61
21-122	Not Leukaemia	1.02	0.98	1.06	0.38	1.02	0.97	1.07	0.39	1.02	0.98	1.07	0.23	1.02	0.98	1.05	0.42
11-122	Total Childhood Cancer	**1.03**	1.00	1.07	0.04	**1.04**	1.00	1.09	0.04	1.03	1.00	1.07	0.06	1.03	1.00	1.07	0.06

[b]OR for each mGray increase in cumulative gamma exposure

ORs in bold are significantly different from 1.00 (P<0.05)

Table 4.3 Comparison of odds ratios for gamma rays using different estimators for radon exposure

Analyses considering cumulative gamma-ray exposure, Carstairs quintile and

a) All radon estimates from HPA/BGS radon mapping - Main analysis (27447 cases)

b) No allowance for radon (27227 cases)

c) Analysis restricted to GridSq/AP radon estimates (the most precise) (23021 cases)

d) Radon estimated from mean for County District (27447 cases)

Exposure period taken as birth to diagnosis

		Main Analysis (All HPA/BGS radon estimates)				No allowance for radon				Restricted to GridSq/AP estimates				Mean for County District			
ICCC3 Codes		OR[b]	95% CI		P	OR[b]	95% CI		P	OR[b]	95% CI		P	OR[b]	95% CI		P
11	Lymphoid Leukaemia	**1.10**	1.02	1.19	0.01	**1.10**	1.02	1.19	0.01	**1.09**	1.00	1.19	0.05	**1.10**	1.02	1.19	0.01
12	Acute Myeloid leukaemia	1.04	0.89	1.21	0.60	1.04	0.89	1.20	0.65	1.09	0.92	1.29	0.32	1.04	0.89	1.20	0.65
13-15	Other Leukaemia	1.19	0.90	1.57	0.23	1.19	0.90	1.57	0.23	1.28	0.94	1.76	0.12	1.19	0.89	1.57	0.24
11-15	Total Leukaemia	**1.09**	1.02	1.17	0.01	**1.09**	1.02	1.17	0.01	**1.10**	1.02	1.18	0.02	**1.09**	1.02	1.17	0.01
21	Hodgkin's disease	1.04	0.93	1.16	0.53	1.04	0.93	1.16	0.53	1.04	0.92	1.18	0.50	1.04	0.93	1.16	0.52
22	Non-Hodgkin Lymphoma	1.04	0.89	1.21	0.61	1.05	0.90	1.22	0.57	1.07	0.91	1.27	0.41	1.05	0.90	1.22	0.56
21-25	Total Lymphona	1.01	0.93	1.09	0.86	1.01	0.93	1.09	0.84	1.01	0.92	1.10	0.83	1.01	0.93	1.09	0.84
11 ,22	Lymph. Leuk. + NHL	**1.09**	1.02	1.16	0.02	**1.09**	1.02	1.17	0.01	**1.08**	1.00	1.17	0.04	**1.09**	1.02	1.17	0.01
11-15, 22	Total Leuk. + NHL	**1.08**	1.02	1.15	0.01	**1.08**	1.02	1.15	0.01	**1.09**	1.02	1.17	0.01	**1.09**	1.02	1.15	0.01
31-36	Brain/CNS (inc. Benign)	1.02	0.96	1.09	0.49	1.02	0.96	1.09	0.48	0.99	0.93	1.06	0.75	1.02	0.96	1.09	0.46
41-122	Other malignant tumours	1.02	0.96	1.08	0.57	1.02	0.96	1.08	0.57	1.01	0.94	1.07	0.84	1.02	0.96	1.08	0.57
21-122	Not Leukaemia	1.02	0.98	1.06	0.38	1.02	0.98	1.06	0.37	1.00	0.96	1.04	0.96	1.02	0.98	1.06	0.36
11-122	Total Childhood Cancer	**1.03**	1.00	1.07	0.04	**1.04**	1.00	1.07	0.04	1.02	0.99	1.06	0.22	**1.04**	1.00	1.07	0.03

[b]OR for each mGray increase in cumulative gamma exposure

ORs in bold are significantly different from 1.00 (P<0.05), ORs in bold and underlined are significantly different from 1 (P<0.01)

Table 4.4 Comparison of gamma ray odds ratio with different latent periods

Cumulative radon exposure, cumulative gamma-ray exposure and quintiles of Carstairs index of deprivation

a) Latent period nine months - Main analysis (27447 cases)

b) Latent period zero (27447 cases)

c) Latent period twelve months (26365 cases)

d) latent period twenty four month (23335 cases)

		latent period 9 months				latent period zero				latent period 12 months				latent period 24 months			
		OR[b]	95% CI		P	OR[b]	95% CI		P	ORb	95% CI		P	OR[b]	95% CI		P
11	Lymphoid Leukaemia	**1.10**	1.02	1.19	0.01	**1.09**	1.02	1.16	0.02	1.10	1.02	1.19	0.01	1.12	1.02	1.23	0.01
12	Acute Myeloid Leukaemia	1.04	0.89	1.21	0.60	1.04	0.90	1.20	0.59	1.04	0.89	1.22	0.59	1.05	0.88	1.25	0.57
13-15	Other Leukaemia	1.19	0.90	1.57	0.23	1.18	0.91	1.53	0.20	1.20	0.90	1.60	0.22	1.19	0.86	1.65	0.30
11-15	Total Leukaemia	**1.09**	1.02	1.17	0.01	**1.08**	1.02	1.15	0.01	1.10	1.02	1.17	0.01	1.11	1.03	1.20	0.01
21	Hodgkin's disease	1.04	0.93	1.16	0.53	1.03	0.93	1.15	0.52	1.04	0.93	1.16	0.54	1.04	0.92	1.17	0.56
22	Non-Hodgkin Lymphoma	1.04	0.89	1.21	0.61	1.04	0.90	1.20	0.60	1.04	0.89	1.22	0.61	1.04	0.88	1.24	0.63
21-25	Total Lymphoma	1.01	0.93	1.09	0.86	1.01	0.93	1.09	0.87	1.01	0.93	1.10	0.86	1.01	0.92	1.10	0.86
11, 22	Lymph. Leuk. + NHL	**1.09**	1.02	1.16	0.02	**1.08**	1.01	1.15	0.02	1.09	1.02	1.17	0.02	1.10	1.02	1.20	0.02
11-15, 22	Total Leuk. + NHL	**1.08**	1.02	1.15	0.01	**1.08**	1.02	1.14	0.01	1.09	1.02	1.16	0.01	1.10	1.02	1.18	0.01
31-36	Brain/CNS (inc. Benign)	1.02	0.96	1.09	0.49	1.02	0.96	1.08	0.47	1.02	0.96	1.09	0.51	1.02	0.95	1.10	0.53
41-122	Other malignant tumours	1.02	0.96	1.08	0.57	1.01	0.96	1.07	0.62	1.02	0.96	1.08	0.54	1.03	0.96	1.10	0.45
21-122	Not Leukaemia	1.02	0.98	1.06	0.38	1.02	0.98	1.05	0.40	1.02	0.98	1.06	0.37	1.02	0.98	1.07	0.34
11-122	Total Childhood Cancer	**1.03**	1.00	1.07	0.04	**1.03**	1.00	1.06	0.04	1.04	1.00	1.07	0.04	1.04	1.00	1.08	0.03

bOR for each mGray increase in cumulative gamma exposure

ORs in bold are significantly different from 1.00 (P<0.05), ORs in bold and underlined are significantly different from 1.00 (P<0.01)

Table 4.5. Cumulative radiation exposure-induced cancer incidence risk (REIC, %) predicted for male UK population (as per Little *et al J Radiol Prot* 2009 29 467-82) exposed to 1 mGy per year (pro rata (0.728 mGy) *in utero*)

Age	UNSCEAR [a]	BEIR VII [b]	Current paper [a,b]
0	0.00000	0.00000	0.00000
1	0.00106	0.00029	0.00035
2	0.00289	0.00078	0.00163
3	0.00462	0.00142	0.00355
4	0.00590	0.00215	0.00550
5	0.00666	0.00282	0.00694
6	0.00728	0.00345	0.00836
7	0.00789	0.00408	0.00999
8	0.00830	0.00460	0.01116
9	0.00867	0.00510	0.01234
10	0.00903	0.00559	0.01361
11	0.00941	0.00609	0.01505
12	0.00974	0.00654	0.01636
13	0.01004	0.00696	0.01758
14	0.01042	0.00744	0.01930

[a] Using a latent period of 2 years, and for the BEIR VII and UNSCEAR models the BEIR VII recommended 30 : 70 excess absolute risk : excess relative risk model weighting

[b] Using regression coefficient from a log-linear logistic model for gamma-ray dose (ERR = 88.82 Gy^{-1}), adjusted using Carstairs quintile.

9 FIGURES

Figure 4.1. Observed (and 95% CI) and fitted relative risk for leukaemia by cumulative gamma-ray dose. The smoothed spline model used to obtain the "observed" fits employs a 5-point moving average over neighbouring points (with weights the product of (0.15, 0.2, 0.3, 0.2, 0.15) and the inverse variance of each point).

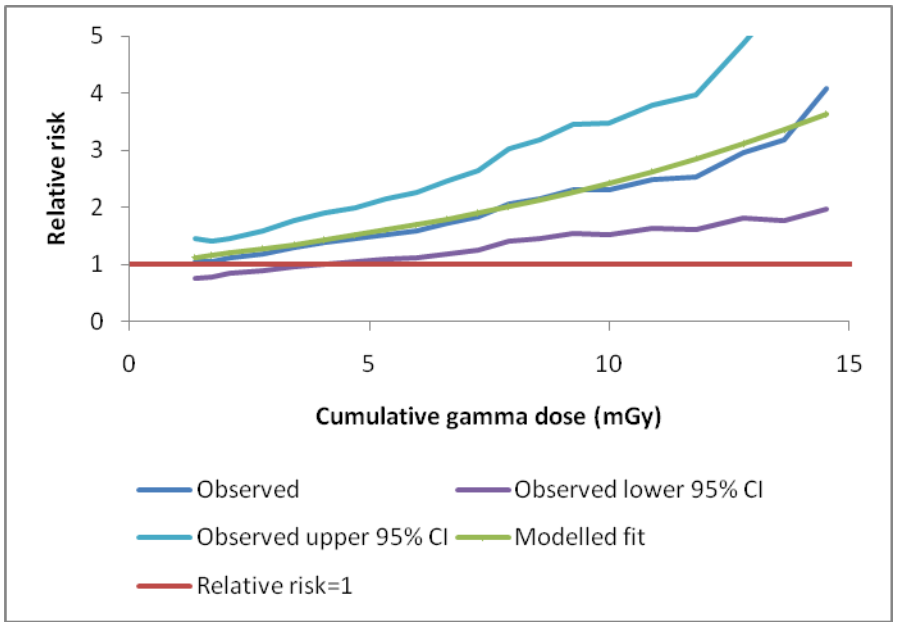
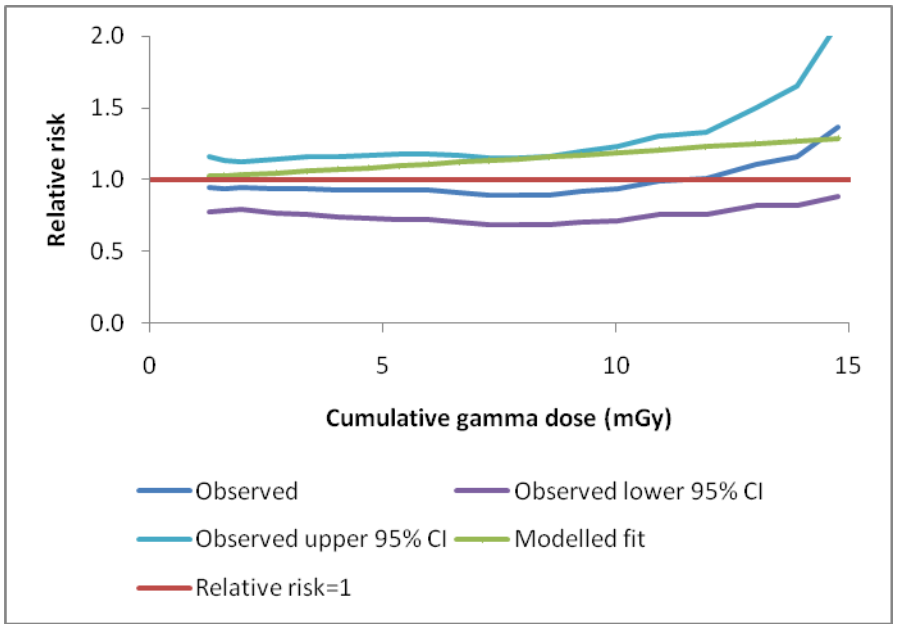


Figure 4.2. Observed (and 95% CI) and fitted relative risk for all cancers except leukaemia by cumulative gamma-ray dose. The smoothed spline model used to obtain the "observed" fits employs a 5-point moving average over neighbouring points (with weights the product of (0.15, 0.2, 0.3, 0.2, 0.15) and the inverse variance of each point).



APPENDIX A Previous epidemiological studies of childhood cancer and natural radiation

A number of epidemiological studies have been carried out in order to investigate the possibility of a link between childhood cancers, in particular leukaemia, and exposure to ionising radiation from natural sources. These have been of case/control or ecological (geographical correlation) design. Case/control studies allow a greater range of data to be collected. However, they are complex and therefore expensive to conduct and may therefore be limited in size. They may also be subject to participation bias. Ecological studies can typically be larger than case/control studies, but lack individual measurements of the risk factor being examined and are potentially subject to the effects of confounding by factors which cannot be allowed for in the analysis. However, ecological studies are most vulnerable when there is a powerful individual risk factor which can act as a potential confounder (as with smoking and lung cancer). No such powerful risk factor is known for childhood leukaemia.

A1 CASE/CONTROL STUDIES

A1.1 Case control study of ALL by Lubin et al 1998 (Lubin *et al.* 1998)

Lubin et al conducted a case/control study in the United States of incidence of acute lymphoblastc leukaemia (ALL) in children under 15 and residential exposure to radon. It was a condition for inclusion that time weighted radon measurements were available for 70% of the 5-year period leading up to diagnosis. The study included 505 cases and 443 age matched controls. The time-weighted radon exposures were 65.4 Bq m^{-3} for cases and 79.1 Bq m^{-3} for controls in the matched analysis and somewhat higher in the unmatched analysis. This is a little higher than in US homes generally because the study was carried out in a relatively high radon area. The levels are much higher than in the UK. Because of the potentially rapid appearance of leukaemia after radiation exposure the analysis was carried out in terms of the time-weighted radon exposure for the whole of the assessment period without a lag interval. Information on potentially confounding factors was collected at interview.

In neither the matched nor the unmatched analysis was there evidence of a higher risk of ALL with higher radon levels. Results were similar in the matched and the unmatched analysis and when a lag period of two years was introduced into the time-weighted radon concentration estimate.

A1.2 Case/control study of AML by Steinbuch et al, 1999 (Steinbuch *et al.* 1999)

Steinbuch et al reported on a case/control study in the United States of AML and exposure to radon. Radon levels were measured using alpha-track detectors placed for one year in the current homes of 173 cases and 254 controls. Time weighted average radon concentrations were evaluated to take account of the time spent in different parts of the

home, but radon concentrations in previous homes were not assessed. Telephone interviews were also conducted with the parents of study participants.

There was no significant dose–response relationship between risk of AML and indoor residential radon exposure when all ages were considered together. However, for children aged less than 2 years at diagnosis, there was an inverse association between radon level and AML risk (P = 0.03). The trend and its significance were similar in the subset who had spent all their life in the same house. For those aged 2 or more at diagnosis the estimated relative risk was increased among those with higher radon exposure (P = 0.07; or P = 0.01 for those who had spent all their life in the same house).

Steibuch et al were cautious in the interpretation of their data: They note that overall, there was no association between residential radon exposure and AML risk in children. They further suggest that the apparent positive association between radon and risk of AML after age 2 must be interpreted cautiously because of the limited sample size available for subgroup analysis and the lack of consistency with other data on effects of radiation levels as low as those observed in study homes.

A1.3 Case/Control study in Germany by Kaletsch et al 1999 (Belson M 2007)

Kaletsch et al conducted a case/control study of radon and childhood cancer in Lower Saxony. There were in 82 cases of leukaemia and 82 cases of solid cancers diagnosed before the 15th birthday and 209 controls. Long term radon measurements were carried out in dwellings where the children had lived for a year or more. Analyses took account of urbanisation, SES, age and sex.

The boundary between higher radon levels and the remainder was prespecified as being 70 Bq m-3, the 90th percentile of the set of all measurements. There was no association between higher radon levels and leukaemia. There was a statistically significant elevation of the Odds Ratio for solid cancers (OR=2.6, 95% CI 0.96-7.13) which was mainly due to 6 CNS tumours (6 cases in the higher category of exposure and 35 in the lower). Kaletsch et al regarded this finding as probably being due to chance.

A1.4 The United Kingdom Childhood Cancer Study (UKCCS), 2002 (UK Childhood Cancer Study Investigators 2000; 2002a; 2002b)

One of the largest of the case/control studies was carried out in the United Kingdom under the auspices of the UK Coordinating Committee on Cancer Research.

The United Kingdom Childhood Cancer Study was a case/control study of cancer in children up to the 15th birthday in Great Britain. Case accrual was on a regional basis over a period between 1991 and 1996. In total 4433 eligible cases were identified. Normally, two controls per case, matched on date of birth, sex and region of residence, were selected from population registers. A total of 11987 controls were selected. Information about cases and controls were obtained from interviews with parents and from their General Practitioners and hospital records. The parents of 87% of cases and of 64% of controls agreed to be interviewed; smaller proportions of cases and controls were lost for other

reasons.. Controls categorised as deprived less likely to participate than more affluent controls. The study population comprised 3838 cases (1461 of which were of acute lymphoblastic leukaemia) and 7629 controls.

The UKCCS was set up to investigate five possible causal factors for childhood cancer. One of these was ionising radiation. Under this broad hypothesis, particular attention was given to radon and terrestrial gamma radiation. All UK addresses where the case or control child had lived for 6 months were targeted for radon and gamma measurements. The current occupants of these dwellings were approached by post with a series of follow-up letters if necessary. Those who agreed to measurements were sent two passive radon detectors and two TLDs to measure gamma rays, together with the directly ionising component of cosmic rays. These were recalled after six months. A correction factor was applied to the radon measurement to allow for the season of the year in which it was carried out.

Radon measurements were completed at the address at diagnosis of 2226 (58% of 3838) interviewed cases and 3773 (49% of 7629) interviewed controls (measurements were completed in 44.5% of all control houses, but radon results are analysed in terms of concentration in the home at diagnosis).

Gamma measurements were completed at the address at diagnosis of 2165 (56% of 3838) interviewed cases and 5086 (67% of 7629) interviewed controls.

There was a clear trend of decreasing childhood cancer risk with increasing radon concentration. Adjustment for deprivation made little difference and the pattern was similar in all diagnostic groups and in all regions. The authors regard this finding as artefactual rather than causal and conclude that socio-economic differences between cases and controls and between first choice controls and those actually interviewed probably account for the observed negative association. They argue that the doses from radon to the red bone marrow are too small to result in any observable association.

There was no trend of childhood cancer risk with indoor gamma ray dose rate. This finding remained for matched and unmatched analyses and with and without adjustment for social deprivation. In analyses for specific diagnostic subgroups a weak and non-significant positive association was observed for CNS tumours, this was ascribed to chance. The authors suggest that variations in gamma ray dose rate are too small for any effect to be observable in a study of the size that they had carried out.

In summary, the UKCCS provided no evidence that natural radiation exposures contributed to childhood cancer. However, it is clear that the findings were substantially affected by participation bias and the authors suggest that the study might have been underpowered to detect an association of the expected magnitude.

A1.5 The Raaschou-Nielsen Study of Domestic Radon and Childhood Cancer in Denmark 2008 (Raaschou-Nielsen *et al* 2008)

Raaschou-Nielsen et al identified 2400 incident cases of leukemia (1153 cases), central nervous system (CNS) tumors (922 cases), and malignant lymphoma (325 cases)

diagnosed in children between 1968 and 1994 in the Danish Cancer Registry. Control children were matched on sex and DOB within one year. Two controls per case were selected from the Danish Central Population Registry for leukaemia, 3 for CNS tumours and 5 for malignant lymphoma. The total number of control children was 6697.

The residential history of cases and controls was ascertained from birth to the age at diagnosis (cases) or the age at diagnosis of the corresponding case (controls). Addresses were obtained from the Central and Local Population Registries. Geographical co-ordinates were obtained for over 90% of all addresses of cases and controls. Radon concentrations were estimated using the method of Andersen et al (Andersen *et al* 2007) which takes account of the construction details of the house. The use of such a predictive model will have led to a degree of misclassification compared to case/control studies with measurements in the homes in question. Radon levels in residences of children and the cumulated exposure of each child were calculated as the product of exposure level and time, for each address occupied during childhood. Children were divided into three exposure groups of cumulated radon exposure with cutoffs at the 50^{th} and 90^{th} percentiles of the combined case/control distributions (0.26×10^3 and 0.89×10^3 Bq/m^3-years respectively)

Cumulative radon exposure was associated with risk for acute lymphoblastic leukemia (ALL), with rate ratios of 1.21 (95% confidence interval = 0.98 –1.49) and 1.63 (1.05–2.53) for the two more highly exposed groups when compared with the lowest. A linear dose-response analysis showed a 56% increase in the rate of ALL per 10^3 Bq/m^3-years increase in exposure. No confidence interval was given. The association with ALL persisted in sensitivity analyses and after adjustment for potential confounders. No association was found with the other types of childhood cancer.

This study was entirely record based and was therefore free of selection bias due to incomplete participation. The authors note that their findings might be due to chance or confounding. However, there was no evidence to support the idea of confounding and the authors conclude that this study suggests that domestic radon exposure increases the risk for ALL during childhood but not for other childhood cancers. The authors concluded that about 9% of childhood ALL in Denmark is due to radon.

A2 ECOLOGICAL STUDIES

A2.1 Geographical correlation study of natural radiation and leukaemia and lymphoma in England and Wales by Alexander et al 1990 (Alexander *et al* 1990)

Alexander et al carried out a correlation study between incidence of ten diagnostic groupings of leukaemia and lymphoma and natural radiation in twenty-two administrative counties of England and Wales from 1984 to 1988. The radiation quantities used were county average radon concentrations and gamma ray dose rates for the address at birth. Alexander et al calculated Spearman rank correlation coefficients between county standardised morbidity ratios and the radiation measures. Most of the cases were in adults, but Alexander et al specifically examined 438 cases of ALL aged 0-14y.

A strong correlation was found between ALL in children and county average radon concentration ($p=0.65$, $p<0.005$). A number of other correlations with radon were significant at the 5% level. These included CLL and Hodgkin disease, not normally thought to be radiosensitive. All correlations with gamma rays were close to zero or negative. Alexander et al were cautious in the interpretation of their findings suggestion that confounding might be playing a part.

A2.2 Henshaw et al 1990: Radon as a causative factor in induction of myeloid leukaemia and other cancers (Henshaw *et al.* 1990)

Henshaw et al examined correlations between cancer incidence and mean radon concentrations in fifteen countries where radon surveys have been carried out. Particular attention was directed to adult acute myeloid leukaemia (AML) because a dosimetric model suggested radon could be a causative factor. Adult melanoma and kidney cancer were also regarded as diseases where radon or its decay products might be a causative factor.

Of particular relevance in the present context, Henshaw et al also examined incidence of certain childhood cancers in thirteen countries in relation to the reported radon concentrations. Significant correlations were reported for all childhood cancers ($p<0.01$) and for leukaemia ($p<0.02$) as well as for certain other types of childhood cancer. A significant association was also reported for leukaemia incidence and indoor gamma rays ($p<0.05$). However, there was a strong correlation between indoor radon concentrations and indoor gamma ray dose rates in the dataset used by Henshaw et al.

Henshaw et al acknowledged certain assumptions in their work notably that national estimates of mean radon concentration applied to the areas for which incidence data were available and that incidence data from different countries might not be comparable. Butland et al re-examined the associations for the seven countries for which the data were most reliable. That between radon and total childhood cancer remainded significant ($p<0.05$) while that for childhood leukaemia dropped out of statistical significance ($0.05 < p < 0.10$)

A2.3 Muirhead et al 1991, 1992: An analysis of childhood leukaemia and natural radiation in Britain (Muirhead *et al* 1991; 1992)

Muirhead et al conducted a correlation study of rates of childhood leukaemia and non Hodgkin lymphoma (NHL) and natural radiation in 459 County Districts (or equivalent administrative areas) in England, Scotland and Wales. The study included about 6,700 cases of childhood leukaemia and non Hodgkin lymphoma from the NRCT for the period 1969-1983. The radiation data included in the analysis were population weighted average indoor and outdoor gamma-ray dose rate and indoor radon gas concentrations for the areas in question.

Rates of leukaemia and NHL were analysed as linear functions of radiation levels using Poisson regression. Different analyses used one, two or three of the radiation terms and with the data grouped or ungrouped. Some analyses included terms to represent county effects in the regression model for district data. Methods developed by Stefanski

(Stefanski 1985) were used to estimate the biases in regression coefficients and their standard errors resulting from measurement errors.

For data at County level, the regression coefficient for radon was positive and for both indoor and outdoor gamma negative (all significance levels $0.05<p<0.10$). If analysed one at a time, all regressions were statistically significant.

For analyses between Districts within Counties the trend was negative for radon and positive for indoor gamma.

For analyses between all County Districts, unadjusted for County, none of the regression coefficients differed from zero.

Using the methods of Stefanski to correct for measurement error on the ungrouped analysis at district level increased regression coeff and associated standard error by 40% for indoor gamma and 60% for radon.

Muirhead et al conclude that the difference between the analysis based on counties and that based on districts within counties indicates that the county level analysis is affected by geographical confounding factors.

A2.4 Analysis of leukaemia incidence in Great Britain by Richardson et al (1995) (Richardson *et al* 1995)

Richardson et al (1995) undertook another analysis of essentially the same leukaemia cases and radiation data as those included in the geographical correlation study of Muirhead et al, 1992. Analyses were conducted using data at the level of the 459 County Districts (CD) in Great Britain.

Socio-economic scores were calculated for each CD based on:

- the proportion of economically active males who are working;
- the proportion of households with a car, and
- the proportion of households which are owner-occupied.

These scores were based on data from the 1971 census for the period 1969-1973, on the 1981 census for the period 1979-1983 and on an average for the period 1974-1978.

Analyses of the geographical variation of childhood leukaemia incidence were carried out using Poisson regressions and also by a hierarchical Bayesian model in which extra-Poisson variability was modelled in terms of spatial and non-spatial components. The main finding was that a main part of the geographical variation was due to a local neighbourhood clustering structure. It was hypothesized that this might be a consequence of "a complex combination of environmental and socio-demographic local characteristics". There was evidence for a positive association of leukaemia incidence with socio-economic score. There was no consistent evidence of a positive association of childhood leukaemia incidence with gamma radiation levels; conversely there was some evidence of an inverse association. There was no consistent evidence of any association with radon levels.

A2.5 Geographical correlation study by Gilman and Knox (1998) (ICRP 2003)

Gilman and Knox conducted a geographical correlation study based on place of birth for about 8500 cases of childhood cancer diagnosed up to age 15 and born in Great Britain between 1953 and 1964. Radiation and SES status were assigned to Demographic Districts on a scale of about 10 km grid squares. Mortality was used as the endpoint for analysis because survival was relatively low during this period and because the mortality data were regarded as more reliable than incidence.

Poisson multiple regression was used to examine the effects of birth density, birth year, mean outdoor gamma radiation, mean indoor gamma radiation, mean indoor radon concentration and SES on the variation in mortality among Demographic Districts. Multiplicative models were fitted in the standard statistical analysis package GLIM. Improvements in goodness of fit were assessed by examining the changes in scaled deviance.

High cancer mortalities were associated with areas characterized as having high social class, higher incomes and good housing conditions, but also with high population densities. Mortalities also increased with increased radon exposure, and the relationship operated independently of the socioeconomic factors.

There was a significant positive linear trend of mortality with increasing radon exposure for all cancers, rate ratio 1.07 (1.02-1.12), and for the solid cancers, 1.08 (1.02-1.15), while a quantitatively similar relationship for the leukaemias and lymphomas, 1.06 (0.99-1.12), just failed to reach statistical significance. Gilman and Knox reported that addition of indoor or outdoor gamma to a model which included radon did not significantly decrease the scaled deviance. The size of the radon effect was such that, compared with the median radon level of 21 Bq.m-3, in areas with radon levels of 63 Bq m-3 the rate ratio for all childhood cancers was 1.11 (95% CI 1.04-1.19). They concluded that in such areas around 10% (95% CI 3-16%) of childhood cancers may be attributable to the high radon levels.

A2.6 Ecological study of radon and acute childhood leukaemia in France by Evrard et al. 2005 (Evrard *et al* 2005)

Evrard et al conducted an ecological study of indoor radon concentration and acute leukaemia incidence in children less than 15 years of age in the 348 geographical units (zones d'emploi, ZE) of France between 1990 and 1998. A total of 4015 cases were obtained from the French National Registry of Childhood Leukaemia and Lymphoma and demographic data were obtained from national censuses. Exposure assessment was based on 13 240 measurements covering the whole country, giving an average of 39 per ZE.

A positive ecological association, on the borderline of statistical significance (P= 0.053), was observed between indoor radon concentration and childhood leukaemia incidence. The association was highly significant for acute myeloid leukaemia (P = 0.004) but not for acute lymphocytic leukaemia (P =0.49). The standardized incidence ratio increased by 7, 3 and 24% for all acute leukaemia, ALL and AML, respectively, when radon concentration increased by 100 Bq/m3.

Evrard et al concluded that there was evidence of a moderate association between indoor radon concentration and childhood acute myeloid leukaemia. Since the association is moderate, this result does not appear inconsistent published case–control studies which may have lacked the power to pick up an association of this size.

A2.7 Ecological study in postcode sectors in Devon and Cornwall by Thorne et al (1996) (Thorne *et al* 1996)

Thorne et al (1996) examined childhood cancer incidence rates in the 113 postcode sectors in Devon and Cornwall where mean radon levels were 100 Bq/m3 or above with those in the 170 postcode sectors where mean radon concentrations were below this level. Cases were accumulated over the period 1976-1985. There were 96 childhood cancers of all types in the high radon postcode sectors and 205 in the low radon postcode sectors. For leukaemias the numbers were 35 and 73 respectively with 10 cases of AML in total.

There was no association between radon exposure and overall rate of childhood malignancy. For AML the rate in the high radon postcode sectors was greater than in the low sectors, but the elevation was not significant (P = 0.11). The incidence rate for neuroblastoma was significantly higher in the high radon postcode sectors (P= 0.02). The authors suggested that this might be due to chance, arising as a result of multiple significane testing.

A2.8 Summary of radon case/control studies

In a study of 505 cases and 443 age matched controls Lubin et al (Lubin *et al* 1998) found no evidence for an association between incidence of acute lymphoblastc leukaemia (ALL) in children under 15 and residential exposure to radon.

In a parallel study of 173 cases of AML and 254 controls Steinbuch et al (Steinbuch *et al* 1999) found no significant dose–response relationship between risk of AML and indoor residential radon exposure when all ages were considered together. However, for children aged less than 2 years at diagnosis, there was an inverse association between radon level and AML risk (P = 0.03). For those aged 2 or more at diagnosis the estimated relative risk was increased among those with higher radon exposure (P = 0.07; or P = 0.01 for those who had spent all their life in the same house).

Kaletsch et al (Belson M 2007) conducted a study of 82 cases of leukaemia and 82 cases of solid cancers diagnosed before the 15th birthday and 209 controls. There was no association between higher radon levels and leukaemia. There was a statistically significant elevation of the Odds Ratio for solid cancers (OR=2.6, 95% CI 0.96-7.13) which was mainly due to 6 CNS tumours (6 cases in the higher category of exposure and 35 in the lower). Kaletsch et al regarded this finding as probably being due to chance.

In the UK Childhood Cancer Study (UK Childhood Cancer Study Investigators 2000; 2002b) (7193} radon measurements were completed at the address at diagnosis of 2226 (58% of 3838) interviewed cases and 3773 (49% of 7629) interviewed controls. There was a clear trend of decreasing childhood cancer risk with increasing radon concentration in all

diagnostic groups and in all regions. The authors regard this finding as artefactual rather than causal and conclude that socio-economic differences between cases and controls and between first choice controls and those actually interviewed probably account for the observed negative association.

Raaschou-Nielsen et al (Raaschou-Nielsen *et al* 2008) studied incident cases of leukemia (1153 cases; 2 controls per case), CNS tumors (922 cases; 5 controls per case), and malignant lymphoma (325 cases; 2 controls per case) diagnosed in children between 1968 and 1994 in the Danish Cancer Registry. Radon concentrations were estimated using a predictive model (Andersen *et al* 2007). Children were divided into three exposure groups of cumulated radon exposure with cutoffs at the 50^{th} and 90^{th} percentiles of the combined case/control distributions. Cumulative radon exposure was associated with risk for acute lymphoblastic leukemia (ALL), with rate ratios of 1.21 (95% confidence interval = 0.98 – 1.49) and 1.63 (1.05–2.53) for the two more highly exposed groups when compared with the lowest. A linear dose-response analysis showed a 56% increase in the rate of ALL per 10^3 Bq/m^3-years increase in exposure. No association was found with the other types of childhood cancer.

A2.9 Summary of gamma case/control studies

In the UK Childhood Cancer Study (UK Childhood Cancer Study Investigators 2002a) gamma measurements were completed at the address at diagnosis of 2165 (56% of 3838) interviewed cases and 5086 (67% of 7629) interviewed controls. There was no trend of childhood cancer risk with indoor gamma ray dose rate. This finding remained for matched and unmatched analyses and with and without adjustment for social deprivation. The authors suggest that variations in gamma ray dose rate are too small for any effect to be observable in a study of the size that they had conducted.

A2.10 Summary of ecological studies of natural radiation

Alexander et al (Alexander *et al* 1990) carried out a correlation study between incidence of leukaemia and lymphoma and natural radiation in twenty-two administrative of England and Wales. The radiation quantities used were county average radon concentrations and gamma ray dose rates for the address at birth. Most of the cases were in adults, but Alexander et al specifically examined 438 cases of ALL aged 0-14y. A strong correlation was found between ALL in children and county average radon concentration ($p=0.65$, $p<0.005$). A number of other correlations with radon were significant at the 5% level. All correlations with gamma rays were close to zero or negative. Alexander et al were cautious in the interpretation of their findings suggestion that confounding might be playing a part.

Muirhead et al (Muirhead *et al* 1991; 1992) conducted a correlation study of rates of childhood leukaemia and non Hodgkin lymphoma (NHL) and natural radiation in 459 County Districts in England, Scotland and Wales. The study included about 6,700 cases of childhood leukaemia and non Hodgkin lymphoma from the NRCT for the period 1969-1983. The radiation data were average indoor and outdoor gamma and indoor radon. For

data at County level, the regression coefficient for radon was positive and for both indoor and outdoor gamma negative (all significance levels $0.05<p<0.10$). For analyses between Districts within Counties the trend was negative for radon and positive for indoor gamma. For analyses between all County Districts, unadjusted for County, none of the regression coefficients differed from zero. Muirhead et al conclude that the difference between the analysis based on counties and that based on districts within counties indicates that the county level analysis is affected by geographical confounding factors.

Gilman and Knox (ICRP 2003) conducted a geographical correlation study based on place of birth for about 8500 deaths from childhood cancer diagnosed up to age 15 and born in Great Britain between 1953 and 1964. Radiation and SES status were assigned to Demographic Districts on a scale of about 10 km grid squares. High cancer mortalities were associated with areas of high social class, but also with high population densities. Mortalities in each diagnostic group also increased with increased radon exposure, and the relationship operated independently of the socioeconomic factors. There was little evidence of an association with gamma rays.

Evrard et al (Evrard *et al* 2005) conducted an ecological study of indoor radon concentration and 4015 cases of acute leukaemia incidence in children less than 15 years of age in the 348 geographical units (zones d'emploi, ZE) of France between 1990 and 1998. Exposure assessment was based on 13 240 measurements covering the whole country, giving an average of 39 per ZE. A positive ecological association, on the borderline of statistical significance ($P= 0.053$), was observed between indoor radon concentration and childhood leukaemia incidence. The association was highly significant for acute myeloid leukaemia ($P = 0.004$) but not for acute lymphocytic leukaemia ($P =0.49$). Evrard et al concluded that there was evidence of a moderate association between indoor radon concentration and childhood acute myeloid leukaemia.

Thorne et al (Thorne *et al* 1996) examined childhood cancer incidence rates over the period 1976-1985 in the 113 postcode sectors in Devon and Cornwall where mean radon levels were 100 Bq/m3 or above with those in the 170 postcode sectors where mean radon concentrations were below this level. There was no association between radon exposure and overall rate of childhood malignancy. For AML there was a non-significant elevation of the rate in the high radon postcode sectors. The incidence rate for neuroblastoma was significantly higher in the high radon postcode sectors ($P= 0.02$). The authors suggested that this might be due to chance, arising as a result of multiple significance testing.

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APPENDIX B The National Registry of Childhood Tumours

B1 BACKGROUND

The National Registry of Childhood Tumours (NRCT) (Stiller 2007) is a population-based registry of cancers diagnosed in residents of Great Britain (England, Scotland and Wales) before their 15th birthday. The NRCT developed from the Oxford Survey of Childhood Cancers (OSCC), a nationwide case-control study designed to investigate a variety of possible aetiological factors for childhood cancer and carried out at Oxford under the direction of Dr Alice Stewart. The NRCT originally included children who died of cancer from 1953 onwards throughout Great Britain, notifications being received through death certificates. Data collection was later extended so that cancer registrations for children diagnosed from 1962 onwards were also obtained. Data for Northern Ireland are included from 1993 onwards, so that the whole of the United Kingdom is now covered.

The NRCT does not itself engage in active case-finding, but ascertains cases from a range of other sources. These sources of information are

National and regional cancer registries

Children's Cancer and Leukaemia Group (formerly UK Children's Cancer Study Group)

Children entering leukaemia clinical trials

Death certificates

Controls matched on sex, approximate date of birth and place of birth registration have been selected from same birth register as the case. As pointed out by Breslow and Day (Breslow and Day 1980) (Section 3.4)

"Some matching factors such as place of residence … represent a complex of factors. Then the purpose of the matching is to eliminate the confounding effect of a range of only vaguely specified variables, since the matching provides a stratification by these variables which would otherwise be difficult to perform because of their indeterminate nature. In these circumstances, matching can be an important way of eliminating bias in the risk estimate"

Initially one control per case was selected for the NRCT by searching through the birth register until a matching control was identified. The search was conducted forwards or backwards for alternate cases. A second control has also been routinely selected for cases diagnosed in later years. Here the first control for the case was found by searching forwards and the second by searching backwards in the birth register. In England and Wales a second control has been selected from 2000 onwards (and for a few late registrations from earlier years). Scottish data were transferred in electronic form earlier than those for England and Wales and Scottish data for years up to 2005 was transferred before the NRCT began requesting two controls per case.

Birth certificates are obtained for cases and controls. These contain a variety of information including addresses at birth and, in most cases, father's occupation.

The address of the mother at the time of the birth of the child is known for both cases and controls. Addresses at diagnosis are also known for cases. Address at diagnosis is the same as address at birth for about half the cases on the NRCT (see main text). In most cases an "Addresspoint" grid reference was obtained for the address at birth of cases and controls. These are notionally accurate to 0.1m. In a minority of cases a grid reference was available only for the postcode within which the address fell. This might happen if, for example, the house in question no longer existed. A postcode typically covers a group of about 15 dwellings. In urban areas these are close together, but rural postcodes may be spread over larger areas. In cases where the Addresspoint was known, the mean separation between the Addresspoint grid references and the centroid of the postcode (used by the Codepoint system) was 90m for cases and 91m for controls. More detailed discussion is given by Martin and Higgs (Martin and Higgs 1997).

Addresses at birth for cases and controls have routinely been assigned an Addresspoint grid reference only in recent years. An exercise was undertaken to assign addresspoint grid references to the historical data. This becomes increasingly difficult for older records and when the study was initiated it was decided that 1980 was the first year for which records were adequately complete. This was because it was regarded as possible that the greater precision of Addresspoint grid references might be important for the analysis.

B2 COMPLETENESS OF THE NRCT

The completeness of the NRCT has varied over time and between regions. However, from the early 1970s it is believed that more than 97% of cases are included in the cancer registration system. Cases are increasingly notified to the NRCT by more than one source (Stiller 2007).

A recent investigation by Kroll et al (Kroll *et al* 2011) applied capture-recapture methods to notifications from cancer registries and specialist clinicians. It was found that cancer registries notified 92–96% of registrations, and specialist clinicians 93%. The overall completeness estimate was 99–100% and was above 97% for all the diagnostic and regional subgroups examined. This analysis depends on independence of the various sources of information. In recent times there is extensive transfer of data in electronic form between the various organisations which contribute data to the NRCT and the assumption of indepencence cannot be fully justified. Nevertheless the conclusion that the NRCT is effectively complete in recent years was supported by an analysis of Hospital Episode Statistics for leukaemia patients from England born in 1998 and diagnosed before 2005 (Kroll *et al* 2011a). A similar conclusion was reached in an earlier assessment of the completeness of the NRCT (Draper *et al.* 1989).

Comparison with the United Kingdom Childhood Cancer Study suggests a good level of completeness of ascertainment by the NRCT, at least in the 1990s. For the two years (1993-1994) in which the UKCCS aimed to ascertain all cases of cancer newly diagnosed

in children resident in Britain, the UKCCS registered 2650 cases, of which 722 were lymphoid leukaemia (Smith *et al.* 2006); the UKCCS Methods paper (UK Childhood Cancer Study Investigators 2000) indicates that only cases born in England, Wales and Scotland were considered. For the same period the NRCT registered 2810 cases born in England, Wales and Scotland of which 726 were lymphoid leukaemia. The sources of ascertainment available to the UKCCS were similar to those used by the NRCT (the somewhat greater number of cases ascertained by the latter is probably a reflection of the fact that the last fraction of cases come through rather slowly).

In summary, while it is impossible to prove that no cases of childhood cancer are being missed by the NRCT, investigations have failed to find any evidence for such a shortfall.

B3 ETHICAL APPROVAL FOR RESEARCH STUDIES

The CCRG/NRCT is a full member of the UK Asociation of Cancer Registries and as such has dispensation via the National Information Governance Board for the accumulation, processing and use for approved purposes of cancer registry data without individual consent. These approved purposes include research for public benefit. In addition, CCRG received ethical approval from the Oxford Research Ethics Committee C in 2007 for a 5 year period to 2012, with the expectation of renewal, for a variety of epidemiological study types which cancer registry data would support.

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APPENDIX C Estimates of radon concentrations in dwellings

C1 INTRODUCTION

Radon concentrations vary widely between apparently identical homes in the same street. The reasons for this variation are thought to be differences in details of floor construction (providing routes for radon entry from the soil) and differences between homes in ventilation and heating (affecting differences in pressures inside and outside the house). Because of this variation, it is not possible to estimate indoor radon concentrations to a high degree of accuracy in the absence of radon measurements in the specific homes concerned. There are, however, large geographical variations in mean indoor radon concentrations, and these allow reasonable estimates to be made of average indoor concentrations, and estimates of the uncertainties on these estimates.

Previous ecological studies of childhood cancer and natural radiation have used estimates of radon concentrations in County Districts (Muirhead *et al.* 1991; 1992). These were based on the results of the National Survey (Wrixon *et al.* 1998). These County District means are simply the radon analogues of the gamma ray estimates used in the ecological studies and in the present work, though only 2093 radon estimates contributed to these County District means. The second source of estimates of the radon concentrations in the homes of cases and of controls was a predictive radon map based on both the results of measurements of radon concentrations in homes and on information about the boundaries between different geological units. This was the result of collaborative work between the Health Protection Agency (HPA) and the British Geological Survey (Appleton and Miles 2010; Miles and Appleton 2005; Miles *et al.* 2007). It offers much more detailed radon predictions than the County District means. In the next section we report on an exercise in which the alternative radon estimates ere tested against the measurements of the National Survey. We then explore the consequences of the different methodologies used in the HPA/BGS mapping and the estimates of Andersen et al (Andersen *et al.* 2007) as used in the case/control study of Raaschou-Neilsen (Raaschou-Nielsen *et al.* 2008).

C2 COMPARISONS OF THE MEASUREMENTS OF THE NATIONAL SURVEY WITH PREDICTED CONCENTRATIONS

In order to assess the accuracy of the predictions of the radon estimates used in this study they were compared against measurements made in the National Survey of Natural Radiation (Wrixon *et al* 1998).

In the National Survey, householders were sent, by post, track-etch detectors to measure radon concentrations and thermoluminescent detectors to measure gamma doses. Radon levels in buildings vary with the difference between the temperature in- and out-doors and radon measurements were made in the main living area and in an occupied bedroom for two successive six month periods so as to obtain a true estimate for the year. Complete sets of measurements were made in 2093 houses across the UK. Because the National

Survey investigated a random sample of homes, it provided population based average values for the UK in a way that later, more targeted measurement campaigns could not, despite the great number of measurements made in such campaigns.

In the present intercomparison, measured radon concentrations at 1727 locations from the National Survey were employed. This total was lower than the total number of measurements because of the exclusion of

45 locations in Northern Ireland

270 locations where AP/Gridsquare predictions could not be made or where there was a relatively large uncertainty in the radon measurement of the National Survey.

51 locations where there was only one measurement in the CD.

These measurements were compared with three predictions.

a The mean of the National Survey radon measurements in this County District excluding the measurement in question ("CD_Mean")
b The HPA/BGS predicted arithmetic mean ("AM1") derived from the geometric mean (GM) using an uncorrected geometric standard deviation (GSD).
c The HPA/BGS predicted arithmetic mean ("AM2") derived from the GM using a GSD corrected for the influence of estimating GSD by Bayesian methods and for measurement error (Miles and Appleton 2005).

The results are shown in Table 1. It can be seen that the AM2 estimates are closer to the measurements than CD_Mean or AM1.

The HPA/BGS predictions are based on about half a million radon in house measurements and also make use of geological boundaries. They are thus based on very much more information than the National Survey Data. On the other hand, the National Survey involved a statistically selected sample of measurement locations and considerable efforts were made to ensure that measurements were made in as many of them as possible. In contrast, the bulk of the measurements on which the HPA/BGS rests are for houses where the householder had come forward to accept the offer of a measurement during a radon campaign. Such volunteers are likely to have higher radon levels than the average in their neighbourhood (Miles 2001).

Accordingly investigations were made to see whether simple adjustments would improve the fit of the predictions to the measured values. For AM2 essentially the optimal fit was obtained by subtracting 5.2 Bq m-3 from the estimates. A very small improvement could be achieved by adding a multiplicative term but the more parsimonious adjustment was judged preferable. The optimal linear function of CD_Mean is very different from the unmodified estimate, probably due to the influence of CDs where there were only two measurements.

Any additive adjustment to radiation estimates used in this study will not affect the calculation of Odds Ratios and identical results would be obtained by using the unadjusted values. However, the adjusted values reproduce more accurately the national average radon concentration determined in the National Survey.

Table C1 Results of the comparison of radon estimates with the measurements of the National Survey

	CD_Mean	AM1		AM2	
Unmodified estimators					
Root MSE	48.36	36.66		36.00	
Optimal linear function of Estimators					
Root MSE	41.03	35.45		35.45	
Gradient	0.22 (0.16,0.27)	0.79 (0.73,0.85)		0.85 (0.79,0.92)	
Intercept	17.92 (15.58,20.25)	-0.82	(-3.28,1.64)	-1.09	(-3.57,1.38)
Optimal constant adjustment to estimators					
Root MSE	48.36	35.94		35.64	
Intercept	0.61 (-1.67,2.89)	-7.23	(-8.93,-5.53)	-5.14	(-6.82,-3.46)

Notes: Root MSE= Square root of the residual mean square

C3 COMPARISON WITH THE HPA/BGS RADON ESTIMATES WITH THOSE OF THE RAASCHOU-NEILSEN STUDY.

The case/control study by Raaschou-Neilsen (Raaschou-Nielsen *et al* 2008) relied on estimated radon concentrations in homes provided by Andersen et al (Andersen *et al* 2007). The estimates were based on a model that took into account simplified geology (35 categories) and data on housing characteristics from the Danish Building and Dwelling Register. Andersen et al estimated that 68% of the true radon concentrations in homes would be expected to be within a factor of 2.0 of the values predicted by Andersen et al's model.

The radon estimates used in the current study were based on detailed mapping of radon potential as described by Miles and Appleton (Miles and Appleton 2005). Appleton and Miles (Appleton and Miles 2010) used the same UK radon map dataset to show that geological information explained 14-37% of the total variation (on the log scale) in radon potential between homes, varying between different parts of the country. This is substantially higher than the proportions found in studies in other countries that were based on less detailed geological maps and smaller numbers of house measurement results (Bossew *et al.* 2008; Kemski *et al.* 2006) which gave proportions of 3.3% to 11.2%. When Appleton et al took into account the spatial variation in radon potential within each geological unit, the proportion of the total variation in radon potential between homes explained by the radon map increased to 34-40%. The ability to account for such a high proportion of the variation between homes is due to the fortunate situation of the UK in having very large numbers of radon measurement results available, accurate spatial coordinates for the homes, digital 1:50,000 scale geological maps, and the development of methods to utilise the data for radon mapping (Miles and Appleton 2005).

The proportion of variation in radon concentrations between homes in the UK that depended on house characteristics was reported as 8.9% by Gunby et al (Gunby *et al.* 1993) and as 9% by Hunter et al (Hunter *et al.* 2009). Information on house characteristics was not available for the current study, as the UK does not have a building register

comparable to the one in Denmark. Radon estimates for homes were therefore based solely on the detailed radon map. In order to calculate the accuracy of radon estimates in terms comparable to those given by Andersen et al (Andersen *et al* 2007), it is necessary to know the overall variation in UK domestic radon concentrations. Gunby et al (Gunby *et al* 1993) analysed the results of the UK national survey of radon in homes and concluded that the distribution is lognormal with a geometric standard deviation of 3.158. If the percentage of variation reported by Appleton and Miles (Appleton and Miles 2010) as being unexplained by the mapping (60-66%) is applied to the GSD of 3.158, the range of residual GSD is 1.89 - 2.08. This, like the value of 2.0 quoted by Andersen et al (Andersen *et al* 2007), is a multiplier implying that 68% of the true radon concentrations in homes would be expected to be within a factor of 1.89 - 2.08 of the values predicted by the model. This estimated accuracy has been tested using the predicted concentrations for locations of National Survey measurements described above. It was found that 68% of the true values were within a factor of 2.05 of the prediction. The accuracy of the estimated radon concentrations in this study is therefore closely comparable with that in Raaschou-Neilsen (Raaschou-Nielsen *et al* 2008).

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APPENDIX D Fuller description of analytical methods

The analysis used conditional logistic regression implemented in STATA. The probability of developing cancer for individual j in stratum i (as given by an indicator variable $Y_{i,j}=1$ if cancer, and $Y_{i,j}=0$ if not) with cumulative lagged dose $D_{i,j}$ (lagged by 9 months in the main analysis, but using also 0, 12 and 24 months in subsidiary analyses) and Carstairs score $S_{i,j}$ is given by the standard logistic model:

$$P[Y_{i,j} \mid D_{i,j}, S_{i,j}] = \frac{\exp\left[\alpha_{0,i} + \alpha_1 D_{i,j} + \alpha_2 S_{i,j}\right]^{Y_{i,j}}}{1+\exp\left[\alpha_{0,i} + \alpha_1 D_{i,j} + \alpha_2 S_{i,j}\right]} \qquad \text{(D1)}$$

Therefore, the odds ratio for the individual j relative to individual j_0 is given by:

$$\frac{\dfrac{P[Y_{i,j}=1 \mid D_{i,j}, S_{i,j}]}{P[Y_{i,j}=0 \mid D_{i,j}, S_{i,j}]}}{\dfrac{P[Y_{i,j_0}=1 \mid D_{i,j_0}, S_{i,j_0}]}{P[Y_{i,j_0}=0 \mid D_{i,j_0}, S_{i,j_0}]}} = \exp\left[\alpha_1[D_{i,j}-D_{i,j_0}]+\alpha_2[S_{i,j}-S_{i,j_0}]\right] \qquad \text{(D2)}$$

Then the conditional probability of individual $j=0$ being the case and individuals $j=1,...,K_i$ being the controls is:

$$P[j=0 \text{ is case}, j=1,...,K_i \text{ are controls} | D_{i,j}, S_{i,j}, j=0,...,K_i] \qquad \text{(D3)}$$

$$= \frac{P\left[Y_{i,0}=1 \mid D_{i,0}, S_{i,0}\right]\prod_{j=1}^{K_i} P\left[Y_{i,j}=0 \mid D_{i,j}, S_{i,j}\right]}{\sum_{j=0}^{K_i} P\left[Y_{i,j}=1 \mid D_{i,j}, S_{i,j}\right]\prod_{m\neq j} P\left[Y_{i,m}=0 \mid D_{i,m}, S_{i,m}\right]}$$

$$= \frac{\exp\left[\alpha_1 D_{i,0} + \alpha_2 S_{i,0}\right]}{\sum_{j=0}^{K_i} \exp\left[\alpha_1 D_{i,j} + \alpha_2 S_{i,j}\right]}$$

In the present study the number of controls is always $K_i=1$ or $K_i=2$. The conditional likelihood is simply the product over all matched case-control sets of these terms. This model was fitted via maximum likelihood.

As in (D2), the odds ratio (which is very close to the relative risk (RR) when the probability of disease is (as here) low) is given by $OR=\exp\left[\alpha_1[D_{i,j}-D_{i,j_0}]+\alpha_2[S_{i,j}-S_{i,j_0}]\right]$. With a slight abuse of notation, we generally present results as RRs relative to the zero dose group, so that $RR=\exp\left[\alpha_1 D_{i,j}\right]$. Confidence intervals (CI) were Wald-based, calculated

using the Fisher information. The p-values presented were calculated from likelihood-ratio tests, and are two-sided. Heterogeneity across strata was assessed by considering the value of the deviance difference statistic (in relation to the chi-squared distribution) with the appropriate number of degrees of freedom for combining the RRs for radon and gamma individually.

APPENDIX E More detailed description of the study population

Table E1 Breakdown of number of cases by ICCC3 code, sex and age at diagnosis in single years.

Table E2 Socio-Economic Status (SES) breakdowns for cases and controls

Table E3 Categories of radon estimates for cases and controls

Table E4 Numbers of cases and controls for all records; records with GridSq/AP radon estimates and records in sets complete in this respect

Table E5 Numbers of cases and controls for all records; for records with father's social class and for records in sets complete in this respect

Table E6 Breakdown by calendar year of the dates of birth and diagnosis of cases and controls.

Table E7 Breakdown by age at diagnosis for cases and controls (cont1, cont2 and all controls).

Table E8 Table of number of cases by grouped ages with mean ages at diagnosis for cases and controls 1 and 2

Table E9 Details of gamma, radon and RBM doses to first and second controls and their matched cases

Table E10 Twoway of age at diagnosis vs cumulative gamma ray dose (mGy) for All Leukaemias

Table E11 Twoway of age at diagnosis vs cumulative gamma ray dose (mGy) for All Other Cancers

Table E12 Twoway of age at diagnosis vs cumulative radon exposure (k Bq m-3 years) for All leukaemia

Table E13 Twoway of age at diagnosis vs cumulative radon exposure (k Bq m-3 years) for All Other Cancers

Table E14 Twoway of Carstairs Quintile vs gamma ray dose (mGy) for All Cancers; data for cases and controls separately

Table E15 Twoway of Carstairs Quintile vs radon cumulative exposure (k Bq m-3 years) for All Cancers; data for cases and controls separately

Table E16 Main analysis for case and control1 pairs also showing RR per Carstairs Quintiles

Table E1a Breakdown of number of cases by ICCC3 code and age at diagnosis in single years for Males

ICCC3	Age at diagnosis in single years															
Code	<1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
11	156	368	707	733	524	372	249	209	150	134	109	90	90	100	94	4085
12	125	112	65	55	34	25	26	37	36	39	29	44	26	28	23	704
13	7	7	2	6	6	3	8	2	1	8	5	4	12	2	9	82
14	35	31	16	15	13	4	8	4	3	2	1	2	0	1	0	135
15	18	5	4	5	3	2	1	3	0	1	1	0	1	1	3	48
21	0	1	5	29	30	32	42	42	40	41	63	54	64	88	85	616
22	10	17	34	60	57	62	50	58	58	48	40	55	35	43	36	663
23	0	0	14	26	36	27	22	32	19	14	26	15	15	21	11	278
24	5	3	0	0	2	0	0	0	1	0	0	0	0	0	1	12
25	0	1	4	2	0	2	1	0	3	1	1	0	2	2	3	22
31	64	102	61	39	18	19	18	9	24	10	13	4	13	8	10	412
32	83	106	134	121	105	106	105	82	104	100	74	76	57	64	58	1375
33	76	89	94	78	66	66	68	62	51	49	44	34	11	19	13	820
34	20	21	28	30	43	40	34	34	26	20	22	13	22	15	9	377
35	24	16	24	25	21	29	21	22	35	31	22	29	28	32	34	393
36	36	15	15	13	9	13	8	10	2	4	10	8	8	4	8	163
41	365	208	191	118	94	50	21	23	14	7	2	6	5	0	1	1105
42	1	0	0	1	2	0	0	0	0	2	0	0	2	0	2	10
51	236	100	83	31	16	9	6	2	0	0	0	3	0	1	1	488
61	149	180	161	128	81	53	36	16	9	8	3	4	3	5	0	836
62	1	0	0	1	1	0	0	0	0	2	4	0	1	1	1	12
63	2	0	0	0	0	0	0	1	0	1	0	0	0	0	0	4
71	61	49	22	7	8	3	3	1	1	1	4	0	1	0	0	161
72	3	2	2	1	1	2	1	3	0	2	0	2	0	1	2	22
73	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0	3
81	0	0	1	4	5	8	8	17	21	19	23	35	19	29	37	226
82	0	0	0	0	1	1	0	0	0	0	2	1	3	0	4	12

ICCC3	Age at diagnosis in single years															
Code	<1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
83	1	2	2	4	11	13	9	12	19	13	12	22	18	28	24	190
84	1	0	0	1	0	0	0	2	0	0	2	1	0	0	2	9
85	1	0	0	1	0	0	2	0	0	0	0	1	0	0	0	5
91	57	72	87	78	80	49	52	29	33	14	15	17	9	6	17	615
92	29	4	4	0	2	3	2	2	2	2	5	0	5	3	6	69
94	34	15	11	19	6	18	13	14	17	16	22	27	24	28	25	289
95	15	5	4	5	2	2	1	3	3	1	4	4	3	3	4	59
101	21	3	7	4	4	6	5	8	8	9	11	18	19	18	19	160
102	42	18	5	2	1	1	0	0	0	0	1	1	1	1	2	75
103	60	84	29	5	3	1	0	0	1	0	2	0	0	1	14	200
104	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1
105	1	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2
111	1	3	2	1	2	0	1	1	0	1	0	0	0	0	0	12
112	0	0	3	1	1	1	3	0	2	6	3	1	3	4	7	35
113	0	0	0	0	0	0	1	1	0	2	2	4	6	2	5	23
114	3	2	4	2	4	4	7	2	5	5	12	7	11	8	9	85
115	1	0	3	3	1	1	6	3	6	1	5	7	5	11	15	68
116	1	2	1	1	1	1	1	3	4	10	4	9	9	12	14	73
121	2	1	2	1	3	0	0	0	0	1	0	2	1	1	0	14
122	11	4	3	4	7	6	1	1	2	4	3	1	4	1	5	57
Total	1760	1648	1835	1660	1304	1034	840	750	700	629	602	601	536	592	614	15105

Table E1b Breakdown of number of cases by ICCC3 code and age at diagnosis in single years for females.

ICCC3	Age at diagnosis in single years															
Code	<1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
11	181	302	598	540	410	269	199	131	105	86	97	74	76	55	59	3182
12	112	126	54	40	35	36	24	27	18	20	20	24	26	30	20	612
13	6	5	3	2	5	5	3	4	4	3	4	8	3	3	3	61
14	27	15	11	8	5	5	3	0	3	2	3	1	4	1	3	91
15	22	13	4	3	3	0	3	4	0	2	0	0	0	3	1	58
21	0	2	4	3	8	17	14	13	14	20	22	22	38	67	79	323
22	4	21	27	25	32	28	18	20	17	12	21	19	23	29	24	320
23	1	1	3	10	5	4	8	9	6	4	4	4	3	6	4	72
24	2	1	0	1	1	0	0	0	0	0	0	0	0	0	0	5
25	1	0	0	1	2	1	0	1	1	1	0	0	0	0	0	8
31	53	56	41	23	18	12	22	19	6	8	8	15	7	7	8	303
32	79	102	116	143	139	111	110	95	84	87	61	70	57	75	54	1383
33	65	65	55	46	46	28	35	40	34	23	24	19	14	10	12	516
34	22	17	16	30	40	40	39	21	26	18	21	15	17	12	4	338
35	26	12	23	18	22	22	31	24	19	26	12	28	26	26	21	336
36	36	18	13	8	11	8	11	12	10	8	7	9	5	6	7	169
41	325	198	156	107	56	42	23	14	4	6	4	1	3	0	4	943
42	1	2	3	0	2	0	1	0	1	0	0	0	1	0	2	13
51	186	126	72	48	17	8	4	2	0	1	0	1	0	0	0	465
61	124	159	149	176	108	72	38	21	6	12	8	9	3	1	1	887
62	0	0	1	0	0	0	0	1	0	0	2	2	2	1	2	11
63	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	1
71	49	26	15	2	3	0	0	2	1	1	1	0	0	0	0	100
72	0	0	0	0	1	1	2	0	1	2	2	4	1	2	3	19
81	0	0	0	1	4	4	9	20	21	22	32	33	34	24	21	225
82	1	0	0	0	0	0	0	0	0	0	0	2	0	1	0	4
83	1	7	4	4	5	13	6	8	9	14	17	19	20	17	18	162

ICCC3	Age at diagnosis in single years															
Code	<1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
84	1	0	0	0	0	1	0	1	0	1	1	1	1	1	1	9
85	1	1	0	0	0	0	0	1	0	1	0	1	1	2	0	8
91	48	61	64	52	32	37	28	19	23	14	5	11	11	13	9	427
92	19	7	4	3	3	2	2	1	6	2	9	4	5	4	5	76
94	27	17	17	9	11	11	12	17	17	16	18	18	20	22	23	255
95	11	4	3	2	5	2	2	4	5	2	2	1	3	1	4	51
101	19	10	6	5	4	3	5	7	7	7	7	11	8	4	1	104
102	78	52	26	11	2	1	2	3	1	1	0	2	2	1	0	182
103	5	2	1	4	2	5	5	6	12	15	8	12	20	29	30	156
104	0	0	0	1	0	2	0	0	0	0	0	1	0	2	2	8
105	0	1	0	0	0	1	0	0	0	0	0	0	0	0	0	2
111	4	6	3	5	4	1	2	0	3	0	0	1	0	1	1	31
112	0	0	1	3	2	4	4	1	4	5	6	6	16	14	16	82
113	0	0	0	0	0	1	0	0	0	0	1	2	1	2	2	9
114	5	3	6	3	7	4	7	8	7	7	8	6	9	17	11	108
115	0	1	0	2	0	3	2	6	2	3	1	5	12	13	7	57
116	0	2	1	2	2	2	3	4	6	5	8	11	10	21	18	95
121	2	2	2	3	1	0	0	1	0	0	1	1	0	1	1	15
122	7	11	5	2	6	1	1	3	3	3	2	5	2	5	4	60
Total	1551	1454	1507	1346	1059	807	678	570	487	460	447	478	484	529	485	12342

Table E1c Breakdown of number of cases by ICCC3 code and age at diagnosis in single years for both sexes together

ICCC3	Age at diagnosis in single years															
Code	<1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
11	337	670	1305	1273	934	641	448	340	255	220	206	164	166	155	153	7267
12	237	238	119	95	69	61	50	64	54	59	49	68	52	58	43	1316
13	13	12	5	8	11	8	11	6	5	11	9	12	15	5	12	143
14	62	46	27	23	18	9	11	4	6	4	4	3	4	2	3	226
15	40	18	8	8	6	2	4	7	0	3	1	0	1	4	4	106
21	0	3	9	32	38	49	56	55	54	61	85	76	102	155	164	939
22	14	38	61	85	89	90	68	78	75	60	61	74	58	72	60	983
23	1	1	17	36	41	31	30	41	25	18	30	19	18	27	15	350
24	7	4	0	1	3	0	0	0	1	0	0	0	0	0	1	17
25	1	1	4	3	2	3	1	1	4	2	1	0	2	2	3	30
31	117	158	102	62	36	31	40	28	30	18	21	19	20	15	18	715
32	162	208	250	264	244	217	215	177	188	187	135	146	114	139	112	2758
33	141	154	149	124	112	94	103	102	85	72	68	53	25	29	25	1336
34	42	38	44	60	83	80	73	55	52	38	43	28	39	27	13	715
35	50	28	47	43	43	51	52	46	54	57	34	57	54	58	55	729
36	72	33	28	21	20	21	19	22	12	12	17	17	13	10	15	332
41	690	406	347	225	150	92	44	37	18	13	6	7	8	0	5	2048
42	2	2	3	1	4	0	1	0	1	2	0	0	3	0	4	23
51	422	226	155	79	33	17	10	4	0	1	0	4	0	1	1	953
61	273	339	310	304	189	125	74	37	15	20	11	13	6	6	1	1723
62	1	0	1	1	1	0	0	1	0	2	6	2	3	2	3	23
63	2	0	0	0	0	0	0	1	1	1	0	0	0	0	0	5
71	110	75	37	9	11	3	3	3	2	2	5	0	1	0	0	261
72	3	2	2	1	2	3	3	3	1	4	2	6	1	3	5	41
73	2	0	1	0	0	0	0	0	0	0	0	0	0	0	0	3
81	0	0	1	5	9	12	17	37	42	41	55	68	53	53	58	451
82	1	0	0	0	1	1	0	0	0	0	2	3	3	1	4	16
83	2	9	6	8	16	26	15	20	28	27	29	41	38	45	42	352

ICCC3	Age at diagnosis in single years															
Code	<1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	Total
84	2	0	0	1	0	1	0	3	0	1	3	2	1	1	3	18
85	2	1	0	1	0	0	2	1	0	1	0	2	1	2	0	13
91	105	133	151	130	112	86	80	48	56	28	20	28	20	19	26	1042
92	48	11	8	3	5	5	4	3	8	4	14	4	10	7	11	145
94	61	32	28	28	17	29	25	31	34	32	40	45	44	50	48	544
95	26	9	7	7	7	4	3	7	8	3	6	5	6	4	8	110
101	40	13	13	9	8	9	10	15	15	16	18	29	27	22	20	264
102	120	70	31	13	3	2	2	3	1	1	1	3	3	2	2	257
103	65	86	30	9	5	6	5	6	13	15	10	12	20	30	44	356
104	0	0	0	1	0	2	0	0	0	0	1	1	0	2	2	9
105	1	1	0	0	0	1	0	0	0	0	0	0	0	0	1	4
111	5	9	5	6	6	1	3	1	3	1	0	1	0	1	1	43
112	0	0	4	4	3	5	7	1	6	11	9	7	19	18	23	117
113	0	0	0	0	0	1	1	1	0	2	3	6	7	4	7	32
114	8	5	10	5	11	8	14	10	12	12	20	13	20	25	20	193
115	1	1	3	5	1	4	8	9	8	4	6	12	17	24	22	125
116	1	4	2	3	3	3	4	7	10	15	12	20	19	33	32	168
121	4	3	4	4	4	0	0	1	0	1	1	3	1	2	1	29
122	18	15	8	6	13	7	2	4	5	7	5	6	6	6	9	117
Total	3311	3102	3342	3006	2363	1841	1518	1320	1187	1089	1049	1079	1020	1121	1099	27447

Table E2 Socio-Economic Status (SES) Breakdown of cases and controls

				Percentages of all records		
	Cases	Controls	Total	Cases	Controls	Total
Histogram of Carstairs Quintiles						
Quintile 1	3315	4367	7682	12	12	12
Quintile 2	3899	5217	9116	14	14	14
Quintile 3	4748	6192	10940	17	17	17
Quintile 4	6281	8413	14694	23	23	23
Quintile 5	9204	12604	21808	34	34	34
Total	27447	36793	64240	100	100	100
Social class based on fathers occupation						
Total with Class Unset	2526	4120	6646	9	11	10
Occupation Unset	1970	3254	5224	7	9	8
Occupation Unclassifiable	556	866	1422	2	2	2
Social Class 1	1952	2466	4418	7	7	7
Social Class 2	6042	7946	13988	22	22	22
Social Class 3N	3193	4133	7326	12	11	11
Social Class 3M	8209	10457	18666	30	28	29
Social Class 4	4101	5602	9703	15	15	15
Social Class 5	1424	2069	3493	5	6	5
All records with Social Class set	24921	32673	57594	91	89	90
Total of all records	27447	36793	64240	100	100	100

Table E3 Details of categories of radon estimate

				Percentages		
Category	Cases	Controls	Total	Cases	Controls	Total
Gridsquare mapping and Addresspoint	24149	32364	56513	88	88	88
Non-gridsq mapping and Addresspoint	2062	2872	4934	8	8	8
Gridsquare mapping and Codepoint	990	1282	2272	4	3	4
Non-gridsq mapping and Codepoint	246	275	521	1	1	1
Total	27447	36793	64240	100	100	100

Table E4 Numbers of cases and controls by ICCC3 coding for all records for records with Gridsq/AP radon estimate and for records in sets which are complete in this respect

		Whole dataset		Records with Gridsq/AP radon		Sets of records with Gridsq/AP radon	
Disease Grouping	ICCC3 Code	Cases	Controls	Cases	Controls	Cases	Controls
Lymphoid leukaemias	11	7267	9571	6551	8612	6089	7895
Acute myeloid leukaemias	12	1316	1737	1182	1570	1113	1440
Other leukaemias	13-15	475	604	425	554	397	510
Total leukaemia	11-15	9058	11912	8158	10736	7599	9845
Hodgkin lymphomas	21	939	1388	847	1248	804	1149
NHL except Burkitt lymphoma	22	983	1302	881	1172	823	1065
All Lymphomas	21-25	2319	3274	2079	2945	1961	2690
Lymphoid leukaemia and NHL	11,22	8250	10873	7432	9784	6912	8960
Total leukaemia and NHL	11-15,22	10041	13214	9039	11908	8422	10910
Brain and CNS tumours	31-36	6585	8997	5957	8128	5589	7501
Other malignant tumours	41-122	9485	12610	8470	11259	7872	10234
All Cancer except leukaemia	21-122	18389	24881	16506	22332	15422	20425
Total childhood Cancer	11-122	27447	36793	24664	33068	23021	30270
Percentage		100	100	90	90	84	82

Table E5 Numbers of records with father's social class set and numbers of these in complete sets

		All records		Fathers Social Class set for record		Fathers Social Class set for both case and control(s)	
Disease Grouping	ICCC3 Code	Cases	Controls	Cases	Controls	Cases	Controls
Lymphoid leukaemias	11	7267	9571	6655	8531	6258	7861
Acute myeloid leukaemias	12	1316	1737	1182	1548	1110	1405
Other leukaemias	13-15	475	604	429	539	401	495
Total leukaemia	11-15	9058	11912	8266	10618	7769	9761
Hodgkin lymphomas	21	939	1388	837	1211	798	1110
NHL except Burkitt lymphoma	22	983	1302	894	1159	853	1072
All Lymphomas	21-25	2319	3274	2089	2892	1994	2660
Lymphoid leukaemia and NHL	11,22	8250	10873	7549	9690	7111	8933
Total leukaemia and NHL	11-15,22	10041	13214	9160	11777	8622	10833
Brain and CNS tumours	31-36	6585	8997	5979	7976	5625	7317
Other malignant tumours	41-122	9485	12610	8587	11187	8053	10208
All Cancer except leukaemia	21-122	18389	24881	16655	22055	15672	20185
Total childhood Cancer	11-122	27447	36793	24921	32673	23441	29946
Percentages of all records				91	89	85	81

Table E6 Distribution by calendar year of birth and of diagnosis for cases and controls (where year of diagnosis for a control is that of the matched case).

Year of birth is given by sex as is year of diagnosis for cases.

For controls, year of diagnosis is given by first (control1) and second (control2) control status

	Year of birth for cases and controls by sex						Year of Diagnosis				
	Cases			Controls			Cases			Controls	
Year	Males	Females	Total	Males	Females	Total	Males	Females	Total	Control1	Control2
1980	660	528	1188	663	524	1187	21	18	39	39	0
1981	614	535	1149	617	550	1167	70	57	127	127	0
1982	690	557	1247	701	556	1257	145	139	284	284	0
1983	637	495	1132	646	501	1147	213	157	370	370	0
1984	689	581	1270	706	597	1303	286	227	513	513	2
1985	750	583	1333	781	597	1378	326	258	584	584	1
1986	745	583	1328	819	658	1477	351	292	643	643	1
1987	780	614	1394	884	713	1597	416	376	792	792	3
1988	747	626	1373	902	749	1651	446	394	840	840	0
1989	778	633	1411	954	795	1749	482	370	852	852	3
1990	777	652	1429	1005	836	1841	573	451	1024	1024	5
1991	788	636	1424	1040	842	1882	611	456	1067	1066	9
1992	781	632	1413	1084	870	1954	632	484	1116	1116	6
1993	706	551	1257	968	732	1700	679	539	1218	1217	9
1994	654	512	1166	956	726	1682	715	612	1327	1326	17
1995	598	493	1091	849	691	1540	736	611	1347	1346	20
1996	580	459	1039	870	702	1572	707	643	1350	1348	22
1997	545	455	1000	902	720	1622	806	577	1383	1381	45
1998	498	427	925	871	729	1600	755	613	1368	1368	42
1999	472	362	834	879	672	1551	747	659	1406	1406	75
2000	422	333	755	824	623	1447	751	576	1327	1316	1210
2001	353	320	673	678	632	1310	743	659	1402	1392	1272
2002	280	240	520	552	460	1012	834	714	1548	1534	1405
2003	251	231	482	489	455	944	760	627	1387	1380	1275
2004	164	182	346	326	365	691	797	630	1427	1416	1319
2005	108	96	204	215	183	398	756	611	1367	1362	1349
2006	38	26	64	73	56	129	747	592	1339	1335	1326
Total	15105	12342	27447	20254	16534	36788	15105	12342	27447	27377	9416

Table E7 Distribution of age at diagnosis of cases and controls (first control, second control and all controls separately)

Age at Diagnosis (years)	Number of cases and controls				Percentage of cases	
	Cases	Control 1	Control 2	All Controls	Control 1	Control 2
<1	3342	3307	919	4226	99	27
1	3086	3100	826	3926	100	27
2	3321	3340	933	4273	101	28
3	3021	2999	883	3882	99	29
4	2345	2363	696	3059	101	30
5	1850	1839	581	2420	99	31
6	1530	1518	501	2019	99	33
7	1312	1315	466	1781	100	36
8	1185	1182	453	1635	100	38
9	1094	1081	458	1539	99	42
10	1056	1039	455	1494	98	43
11	1068	1077	511	1588	101	48
12	1027	1014	496	1510	99	48
13	1120	1114	608	1722	99	54
14	1090	1089	630	1719	100	58
Total	27447	27377	9416	36793	100	34

Table E8 Number of cases and controls by grouped ages and mean ages

First controls and their matched cases analysed separately from second controls and their matched cases

		Number of records in age group					Mean ages	
Disease Grouping	ICCC3 Code	<1Y	1-4Y	5-9Y	10-14Y	All Ages	Cases	Controls
First controls and their matching case								
Lymphoid leukaemias	11	337	4171	1905	836	7249	5.1	5.0
Acute myeloid leukaemias	12	240	516	290	268	1314	5.2	5.2
Other leukaemias	13-15	118	188	91	77	474	4.6	4.6
Total leukaemia	11-15	695	4875	2286	1181	9037	5.1	5.1
Hodgkin lymphomas	21	0	84	274	577	935	10.5	10.5
NHL except Burkitt lymphoma	22	14	273	371	322	980	7.8	7.8
All Lymphomas	21-25	23	469	803	1017	2312	8.9	8.9
Lymphoid leukaemia and NHL	11,22	351	4444	2276	1158	8229	5.4	5.4
Total leukaemia and NHL	11-15,22	709	5148	2657	1503	10017	5.3	5.3
Brain and CNS tumours	31-36	588	2339	2232	1406	6565	6.2	6.2
Other malignant tumours	41-122	2021	4089	1628	1725	9463	4.8	4.8
All Cancer except leukaemia	21-122	2632	6897	4663	4148	18340	5.8	5.8
Total childhood Cancer	11-122	3327	11772	6949	5329	27377	5.6	5.6
Second controls and their matching case								
Lymphoid leukaemias	11	91	1168	656	407	2322	5.8	5.8
Acute myeloid leukaemias	12	66	133	103	121	423	6.4	6.4
Other leukaemias	13-15	30	38	26	36	130	5.9	5.9
Total leukaemia	11-15	187	1339	785	564	2875	5.9	5.9
Hodgkin lymphomas	21	0	29	111	313	453	11.1	11.1
NHL except Burkitt lymphoma	22	4	60	105	153	322	9.1	9.1
All Lymphomas	21-25	6	134	293	529	962	9.8	9.8
Lymphoid leukaemia and NHL	11,22	95	1228	761	560	2644	6.2	6.2
Total leukaemia and NHL	11-15,22	191	1399	890	717	3197	6.2	6.2
Brain and CNS tumours	31-36	155	758	801	718	2432	7.1	7.1
Other malignant tumours	41-122	581	1097	582	887	3147	6.0	6.0
All Cancer except leukaemia	21-122	742	1989	1676	2134	6541	7.0	7.0
Total childhood Cancer	11-122	929	3328	2461	2698	9416	6.6	6.6
All controls and cases								
Lymphoid leukaemias	11	428	5339	2561	1243	9571	5.1	5.2
Acute myeloid leukaemias	12	306	649	393	389	1737	5.2	5.5
Other leukaemias	13-15	148	226	117	113	604	4.7	4.9
Total leukaemia	11-15	882	6214	3071	1745	11912	5.1	5.3
Hodgkin lymphomas	21	0	113	385	890	1388	10.6	10.7
NHL except Burkitt lymphoma	22	18	333	476	475	1302	7.8	8.1
All Lymphomas	21-25	29	603	1096	1546	3274	8.9	9.2
Lymphoid leukaemia and NHL	11,22	446	5672	3037	1718	10873	5.4	5.6
Total leukaemia and NHL	11-15,22	900	6547	3547	2220	13214	5.3	5.5
Brain and CNS tumours	31-36	743	3097	3033	2124	8997	6.3	6.5
Other malignant tumours	41-122	2602	5186	2210	2612	12610	4.8	5.1
All Cancer except leukaemia	21-122	3374	8886	6339	6282	24881	5.8	6.1
Total childhood Cancer	11-122	4256	15100	9410	8027	36793	5.6	5.8

Table E9 Cumulative exposure and RBM equivalent dose from birth to diagnosis to first (Control1) and second (Control2) controls and their matched cases

	Case/Control1 pairs		Case/Control2 pairs	
	Cases	Controls	Cases	Controls
Number of records	27377	27377	9416	9416
Radon				
Mean cumulative exposure (kBq m^{-3})	0.12	0.12	0.15	0.14
Mean RBM equivalent dose (mSv)	0.41	0.40	0.49	0.48
Gamma-ray				
Mean cumulative exposure (mGy)	4.64	4.63	5.51	5.50
Mean RBM equivalent dose (mSv)	3.65	3.64	4.33	4.33
Radon and gamma-ray combined				
Mean RBM equivalent dose (mSv)	4.05	4.04	4.82	4.81
Minimum RBM equivalent dose (mSv)	0.00	0.00	0.00	0.00
Maximum RBM equivalent dose (mSv)	31.53	31.53	29.82	29.82

Table E10 Twoway table of age at diagnosis vs cumulative gamma ray dose (mGy) for All Leukaemias

	Dose category																
Age	<1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	>14	Total
Cases																	
<1	689	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	689
1	216	758	10	0	0	0	0	0	0	0	0	0	0	0	0	0	984
2	2	604	830	28	0	0	0	0	0	0	0	0	0	0	0	0	1464
3	0	56	767	564	20	0	0	0	0	0	0	0	0	0	0	0	1407
4	0	9	161	533	322	13	0	0	0	0	0	0	0	0	0	0	1038
5	0	2	13	149	330	215	12	0	0	0	0	0	0	0	0	0	721
6	0	0	1	23	141	221	121	13	3	1	0	0	0	0	0	0	524
7	0	0	1	4	47	118	141	95	13	1	1	0	0	0	0	0	421
8	0	0	1	0	11	46	94	93	63	12	0	0	0	0	0	0	320
9	0	0	0	1	4	11	74	57	88	49	11	2	0	0	0	0	297
10	0	0	0	1	0	3	16	54	70	77	36	10	2	0	0	0	269
11	0	0	0	0	2	1	6	31	45	45	62	41	11	3	0	0	247
12	0	0	0	0	1	2	2	10	35	50	34	59	30	13	0	2	238
13	0	0	0	0	1	0	0	6	21	28	36	50	43	26	7	6	224
14	0	0	0	0	1	0	1	7	7	14	28	41	37	45	24	10	215
Total	907	1429	1784	1303	880	630	467	366	345	277	208	203	123	87	31	18	9058
Controls																	
<1	881	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	882
1	264	949	11	0	0	0	0	0	0	0	0	0	0	0	0	0	1224
2	3	787	1047	28	0	0	0	0	0	0	0	0	0	0	0	0	1865
3	0	86	961	720	32	0	0	0	0	0	0	0	0	0	0	0	1799
4	0	13	186	682	424	19	2	0	0	0	0	0	0	0	0	0	1326
5	0	3	22	202	441	282	13	0	0	0	0	0	0	0	0	0	963
6	0	0	5	35	194	248	180	20	5	0	0	0	0	0	0	0	687
7	0	0	1	6	53	174	176	134	13	2	0	1	0	0	0	0	560
8	0	0	1	2	17	68	135	117	88	13	0	1	0	0	0	0	442
9	0	0	0	2	12	15	86	102	113	79	10	0	0	0	0	0	419
10	0	0	0	2	1	3	25	75	94	106	58	10	3	0	0	0	377
11	0	0	0	1	2	0	18	51	55	70	78	58	12	7	0	0	352
12	0	0	0	0	2	1	4	20	57	57	56	78	43	19	1	2	340
13	0	0	0	0	1	0	1	5	31	55	51	74	75	34	14	5	346
14	0	0	0	0	1	0	3	7	9	37	48	65	48	75	28	9	330
Total	1148	1839	2234	1680	1180	810	643	531	465	419	301	287	181	135	43	16	11912

Table E11 Twoway table of age at diagnosis vs cumulative gamma ray dose (mGy) for All Other Cancers

	Dose category																
Age	<1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	>14	Total
Cases																	
<1	2611	11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2622
1	543	1557	18	0	0	0	0	0	0	0	0	0	0	0	0	0	2118
2	7	866	973	30	2	0	0	0	0	0	0	0	0	0	0	0	1878
3	0	52	873	644	30	0	0	0	0	0	0	0	0	0	0	0	1599
4	0	8	204	661	427	23	2	0	0	0	0	0	0	0	0	0	1325
5	0	2	27	266	472	326	22	5	0	0	0	0	0	0	0	0	1120
6	0	0	11	59	267	369	255	24	7	2	0	0	0	0	0	0	994
7	0	0	6	9	93	264	297	201	26	1	2	0	0	0	0	0	899
8	0	0	2	3	30	152	226	244	186	20	3	1	0	0	0	0	867
9	0	0	0	2	4	42	135	210	232	135	22	7	3	0	0	0	792
10	0	0	0	4	1	24	71	153	167	193	127	30	6	3	0	1	780
11	0	0	0	4	4	3	24	88	159	188	201	137	17	4	1	2	832
12	0	0	0	0	2	2	17	48	109	119	159	184	109	26	5	2	782
13	0	0	0	0	1	1	5	35	76	119	152	128	203	129	36	12	897
14	0	0	0	0	1	3	1	16	38	91	121	147	123	187	120	36	884
Total	3161	2496	2114	1682	1334	1209	1055	1024	1000	868	787	634	461	349	162	53	18389
Controls																	
<1	3357	17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3374
1	675	1991	20	0	0	0	0	0	0	0	0	0	0	0	0	0	2686
2	5	1103	1254	25	0	0	0	0	0	0	0	0	0	0	0	0	2387
3	0	81	1142	846	27	2	0	0	0	0	0	0	0	0	0	0	2098
4	0	7	245	905	526	27	5	0	0	0	0	0	0	0	0	0	1715
5	0	6	38	328	667	399	22	6	0	0	0	0	0	0	0	0	1466
6	0	0	10	70	386	493	346	30	7	2	0	0	0	0	0	0	1344
7	0	0	6	11	141	345	405	259	41	4	1	0	0	0	0	0	1213
8	0	0	5	6	37	178	333	357	238	32	3	2	0	0	0	0	1191
9	0	0	0	7	13	74	177	269	350	189	30	13	3	0	0	0	1125
10	0	0	0	1	0	38	97	228	262	272	175	38	10	2	0	1	1124
11	0	0	0	1	8	6	40	137	236	293	291	175	26	8	4	0	1225
12	0	0	0	0	5	3	18	76	165	191	224	288	158	37	6	6	1177
13	0	0	0	0	1	7	5	50	122	194	232	212	304	184	50	15	1376
14	0	0	0	0	2	3	4	19	74	142	169	224	227	281	191	44	1380
Total	4037	3205	2720	2200	1813	1575	1452	1431	1495	1319	1125	952	728	512	251	66	24881

Table E12 Twoway table of age at diagnosis vs cumulative radon exposure (k Bq m^{-3} years) for all leukaemia

	Cumulative radon exposure (k Bqm^{-3} y)												
Age	<0.05	0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5	>0.5	Total
Cases													
<1	678	8	2	1	0	0	0	0	0	0	0	0	689
1	830	125	15	9	5	0	0	0	0	0	0	0	984
2	939	389	81	20	12	6	3	3	1	0	1	9	1464
3	650	537	140	35	22	7	4	4	3	1	1	3	1407
4	319	410	176	64	29	8	5	5	6	4	4	8	1038
5	124	286	154	70	35	18	15	5	1	1	6	6	721
6	57	190	129	62	29	22	8	4	4	4	2	13	524
7	35	130	102	69	28	15	14	9	2	5	3	9	421
8	22	95	57	61	36	17	10	4	1	5	3	9	320
9	12	73	58	50	36	26	10	12	5	2	1	12	297
10	9	49	65	47	34	22	11	12	8	3	1	8	269
11	5	31	45	35	40	32	16	10	3	8	6	16	247
12	5	34	35	32	37	26	16	15	7	10	2	19	238
13	1	31	50	29	30	24	19	9	9	1	2	19	224
14	0	9	47	30	28	14	25	16	9	5	5	27	215
Total	3686	2397	1156	614	401	237	156	108	59	49	37	158	9058
Controls													
<1	868	10	2	1	1	0	0	0	0	0	0	0	882
1	1022	167	17	3	9	3	0	1	1	0	1	0	1224
2	1188	512	97	30	16	6	3	3	1	2	0	7	1865
3	838	671	172	54	28	9	4	6	4	6	2	5	1799
4	404	540	205	85	41	17	6	5	5	7	3	8	1326
5	167	381	199	105	53	23	14	9	4	1	0	7	963
6	75	231	156	97	40	27	17	11	9	3	5	16	687
7	47	162	155	86	50	27	10	7	2	2	3	9	560
8	22	123	110	71	44	27	18	8	4	4	2	9	442
9	15	108	64	92	50	38	15	11	5	6	0	15	419
10	7	68	98	72	47	21	14	14	9	8	3	16	377
11	9	51	57	64	58	39	17	14	9	4	4	26	352
12	7	48	67	47	49	35	28	22	12	6	4	15	340
13	4	42	54	63	47	35	20	29	13	9	7	23	346
14	1	31	52	51	33	40	29	21	16	16	10	30	330
Total	4674	3145	1505	921	566	347	195	161	94	74	44	186	11912

Table E13 Twoway table of age at diagnosis vs cumulative radon exposure (k Bq m^{-3} years) for All Other Cancers

Cases	Dose category																
Age	<1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	>14	Total
<1	2611	11	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2622
1	543	1557	18	0	0	0	0	0	0	0	0	0	0	0	0	0	2118
2	7	866	973	30	2	0	0	0	0	0	0	0	0	0	0	0	1878
3	0	52	873	644	30	0	0	0	0	0	0	0	0	0	0	0	1599
4	0	8	204	661	427	23	2	0	0	0	0	0	0	0	0	0	1325
5	0	2	27	266	472	326	22	5	0	0	0	0	0	0	0	0	1120
6	0	0	11	59	267	369	255	24	7	2	0	0	0	0	0	0	994
7	0	0	6	9	93	264	297	201	26	1	2	0	0	0	0	0	899
8	0	0	2	3	30	152	226	244	186	20	3	1	0	0	0	0	867
9	0	0	0	2	4	42	135	210	232	135	22	7	3	0	0	0	792
10	0	0	0	4	1	24	71	153	167	193	127	30	6	3	0	1	780
11	0	0	0	4	4	3	24	88	159	188	201	137	17	4	1	2	832
12	0	0	0	0	2	2	17	48	109	119	159	184	109	26	5	2	782
13	0	0	0	0	1	1	5	35	76	119	152	128	203	129	36	12	897
14	0	0	0	0	1	3	1	16	38	91	121	147	123	187	120	36	884
Total	3161	2496	2114	1682	1334	1209	1055	1024	1000	868	787	634	461	349	162	53	18389
Controls																	
<1	3357	17	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3374
1	675	1991	20	0	0	0	0	0	0	0	0	0	0	0	0	0	2686
2	5	1103	1254	25	0	0	0	0	0	0	0	0	0	0	0	0	2387
3	0	81	1142	846	27	2	0	0	0	0	0	0	0	0	0	0	2098
4	0	7	245	905	526	27	5	0	0	0	0	0	0	0	0	0	1715
5	0	6	38	328	667	399	22	6	0	0	0	0	0	0	0	0	1466
6	0	0	10	70	386	493	346	30	7	2	0	0	0	0	0	0	1344
7	0	0	6	11	141	345	405	259	41	4	1	0	0	0	0	0	1213
8	0	0	5	6	37	178	333	357	238	32	3	2	0	0	0	0	1191
9	0	0	0	7	13	74	177	269	350	189	30	13	3	0	0	0	1125
10	0	0	0	1	0	38	97	228	262	272	175	38	10	2	0	1	1124
11	0	0	0	1	8	6	40	137	236	293	291	175	26	8	4	0	1225
12	0	0	0	0	5	3	18	76	165	191	224	288	158	37	6	6	1177
13	0	0	0	0	1	7	5	50	122	194	232	212	304	184	50	15	1376
14	0	0	0	0	2	3	4	19	74	142	169	224	227	281	191	44	1380
Total	4037	3205	2720	2200	1813	1575	1452	1431	1495	1319	1125	952	728	512	251	66	24881

Table E14 Twoway table of Carstairs Quintile vs gamma ray dose (mGy) for All Cancers Case

	Dose category (mGy)																
Cases	<1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	>14	Total
1	497	529	490	349	274	211	196	175	165	150	99	67	55	39	15	4	3315
%	15	16	15	11	8	6	6	5	5	5	3	2	2	1	0	0	100
2	598	570	576	469	338	246	214	199	175	153	123	103	59	43	22	11	3899
%	15	15	15	12	9	6	5	5	4	4	3	3	2	1	1	0	100
3	758	673	708	478	367	302	256	220	218	190	191	162	106	69	34	16	4748
%	16	14	15	10	8	6	5	5	5	4	4	3	2	1	1	0	100
4	878	902	905	697	494	429	356	319	308	260	240	211	123	103	39	17	6281
%	14	14	14	11	8	7	6	5	5	4	4	3	2	2	1	0	100
5	1337	1251	1219	992	741	651	500	477	479	392	342	294	241	182	83	23	9204
%	15	14	13	11	8	7	5	5	5	4	4	3	3	2	1	0	100
Total	4068	3925	3898	2985	2214	1839	1522	1390	1345	1145	995	837	584	436	193	71	27447
%	15	14	14	11	8	7	6	5	5	4	4	3	2	2	1	0	100
Controls																	
1	619	621	630	478	362	284	264	254	242	206	139	113	74	56	19	6	4367
%	14	14	14	11	8	7	6	6	6	5	3	3	2	1	0	0	100
2	805	789	736	551	410	320	277	289	272	234	174	156	102	64	33	5	5217
%	15	15	14	11	8	6	5	6	5	4	3	3	2	1	1	0	100
3	884	884	814	682	511	397	358	341	301	296	250	191	130	97	42	14	6192
%	14	14	13	11	8	6	6	6	5	5	4	3	2	2	1	0	100
4	1164	1145	1134	884	667	540	487	419	464	397	350	310	204	159	67	22	8413
%	14	14	13	11	8	6	6	5	6	5	4	4	2	2	1	0	100
5	1713	1605	1640	1285	1043	844	709	659	681	605	513	469	399	271	133	35	12604
%	14	13	13	10	8	7	6	5	5	5	4	4	3	2	1	0	100
Total	5185	5044	4954	3880	2993	2385	2095	1962	1960	1738	1426	1239	909	647	294	82	36793
%	14	14	13	11	8	6	6	5	5	5	4	3	2	2	1	0	100

Table E15 Twoway table of Carstairs Quintile vs radon cumulative exposure (k Bq m^{-3} years) for All Cancers

Number and percentage of Cases

	Exposure Category (k Bqm-3 y)												
Carstairs	<0.05	0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5	0.55	Total
1	1128	796	465	287	177	123	98	54	41	23	25	98	3315
%	34	24	14	9	5	4	3	2	1	1	1	3	100
2	1342	886	531	346	243	134	108	78	53	29	23	126	3899
%	34	23	14	9	6	3	3	2	1	1	1	3	100
3	1730	1043	608	400	265	186	130	86	51	51	29	169	4748
%	36	22	13	8	6	4	3	2	1	1	1	4	100
4	2418	1450	830	526	321	248	152	77	53	39	25	142	6281
%	38	23	13	8	5	4	2	1	1	1	0	2	100
5	4293	2156	1146	608	387	230	114	87	52	30	26	75	9204
%	47	23	12	7	4	2	1	1	1	0	0	1	100
Total	10911	6331	3580	2167	1393	921	602	382	250	172	128	610	27447
%	40	23	13	8	5	3	2	1	1	1	0	2	100

Number and percentage of Controls

1	1388	1031	596	402	285	187	127	107	56	43	21	124	4367
%	32	24	14	9	7	4	3	2	1	1	0	3	100
2	1804	1109	694	484	311	225	162	114	76	51	33	154	5217
%	35	21	13	9	6	4	3	2	1	1	1	3	100
3	2144	1349	809	538	383	272	183	109	88	83	44	190	6192
%	35	22	13	9	6	4	3	2	1	1	1	3	100
4	3100	1895	1158	733	495	307	224	101	76	74	54	196	8413
%	37	23	14	9	6	4	3	1	1	1	1	2	100
5	5557	3020	1557	902	527	374	202	145	76	62	36	146	12604
%	44	24	12	7	4	3	2	1	1	0	0	1	100
Total	13993	8404	4814	3059	2001	1365	898	576	372	313	188	810	36793
%	38	23	13	8	5	4	2	2	1	1	1	2	100

Table E16 As main analysis but using case and first control pairs only

Model includes cumulative radon exposure, cumulative gamma-ray exposure and quintiles of Carstairs index of deprivation

Exposure period taken as birth to diagnosis

				Relative Risk											
				Radon				Gamma				Carstairs Quintiles			
ICCC3 codes	Diagnostic grouping	Number of Cases	Number of Controls	RRa	95% CI		p	RRb	95% CI		p	RRc	95% CI		p
11	Lymphoid Leukaemia	7249	7249	1.22	0.90	1.65	0.19	**1.12**	1.03	1.21	0.007	**0.96**	0.94	0.99	0.005
12	Acute Myeloid Leukaemia	1314	1314	0.83	0.41	1.70	0.61	1.00	0.85	1.17	0.99	0.95	0.89	1.02	0.16
13-15	Other Leukaemia	474	474	1.27	0.42	3.83	0.67	1.22	0.89	1.67	0.21	1.10	0.99	1.23	0.09
11-15	Total Leukaemia	9037	9037	1.15	0.88	1.49	0.30	**1.10**	1.02	1.18	0.010	**0.97**	0.94	0.99	0.008
21	Hodgkin's disease	935	935	1.38	0.73	2.60	0.32	0.99	0.87	1.12	0.85	1.03	0.95	1.12	0.42
22	Non-Hodgkin Lymphoma	980	980	1.58	0.74	3.38	0.24	1.13	0.96	1.32	0.15	**1.09**	1.00	1.18	0.04
21-25	Total Lymphoma	2312	2312	1.38	0.89	2.15	0.15	1.01	0.92	1.11	0.80	**1.05**	1.00	1.11	0.05
11 ,22	Lymphoid Leukaemia + NHL	8229	8229	1.26	0.95	1.66	0.11	**1.12**	1.04	1.21	0.002	0.97	0.95	1.00	0.05
11-15, 22	Total Leukaemia + NHL	10017	10017	1.19	0.92	1.52	0.18	**1.10**	1.03	1.18	0.003	0.98	0.95	1.00	0.06
31-36	Brain/CNS (including Benign)	6565	6565	1.06	0.79	1.42	0.70	1.04	0.97	1.11	0.27	0.98	0.95	1.01	0.14
41-122	Other malignant tumours	9463	9463	0.96	0.76	1.20	0.70	1.01	0.95	1.07	0.76	0.98	0.96	1.00	0.11
21-122	Not Leukaemia	18340	18340	1.04	0.88	1.23	0.64	1.02	0.98	1.06	0.33	0.99	0.97	1.01	0.18
11-122	Total Childhood Cancer	27377	27377	1.07	0.93	1.23	0.34	**1.04**	1.00	1.08	0.03	**0.98**	0.97	1.00	0.009

[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

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)

APPENDIX F Biasing effects of loss of power due to cases and controls being assigned the same gamma ray dose rate

It is normally considered that a power calculation is unnecessary for a completed epidemiological study such as this, where the confidence interval on the findings indicates the range of odds ratios which are statistically probable. A power calculation relates to hypothetical repetitions of the study and the probability that these produce a significant result, and as such has little to say about the actual data that have been collected. Nevertheless, a power calculation may provide some insight into the possibility that the results obtained are biased – as shown by Land (Land 1980), a statistically significant result from a severely underpowered study is more likely to be biased.

Following the methodology of Little *et al* (Little *et al* 2010), the power for a case-control study having one or two controls per case of this size and with a distribution of gamma ray doses following that for County Districts indicates that the power to detect an association between radiation dose and leukaemia significant at the 5% level is about 68%. However, in the present study approaching half the cases are assigned the same gamma-ray absorbed dose rate as their control(s) and these cases contribute power to the analysis only to the extent that the at-risk period differs between cases and controls. The predicted power of this study is thus hard to assess precisely, but is likely to be about 50%.

If in a study some statistic Z is measured, and it is thought that it has mean Z_0 (the "true" value) and standard deviation σ, then if the power is p with respect to a 1-sided test of size α (of departure from 0) then:

$$p = P\left[\frac{Z}{\sigma} > N_{1-\alpha}\right] = P\left[\frac{Z - Z_0}{\sigma} > N_{1-\alpha} - \frac{Z_0}{\sigma}\right] = P\left[N(0,1) > N_{1-\alpha} - \frac{Z_0}{\sigma}\right],$$

where $N_{1-\alpha}$ satisfies $1-\alpha = P\left[N(0,1) < N_{1-\alpha}\right] = \Phi(N_{1-\alpha})$ and $N(0,1)$ is a standard normal random variable.

This implies that $1-p = P\left[N(0,1) < N_{1-p}\right] = P\left[N(0,1) < N_{1-\alpha} - \frac{Z_0}{\sigma}\right]$, so that $Z_0 = \sigma[N_{1-\alpha} - N_{1-p}]$.

Therefore if $\frac{Z}{\sigma} > N_{1-\alpha}$ we must have that $Z > Z_0 + \sigma N_{1-p}$.

The expected "bias", conditional on the statistic, Z, being statistically significantly greater than 0 ($\frac{Z}{\sigma} > N_{1-\alpha}$), is then the average of all Z above $Z_0 + \sigma N_{1-p}$, or:

$$\frac{\frac{1}{\sigma\sqrt{2\pi}}\int_{Z_0+\sigma N_{1-p}}^{\infty}(x-Z_0)\exp[-(x-Z_0)^2/2\sigma^2]d \quad x}{\frac{1}{\sigma\sqrt{2\pi}}\int_{Z_0+\sigma N_{1-p}}^{\infty}\exp[-(x-Z_0)^2/2\sigma^2]dx} = \frac{\frac{\sigma}{\sqrt{2\pi}}\exp[-{N_{1-p}}^2/2]}{1-\Phi(N_{1-p})}$$

However, as pointed out by Land (Land 1980), the critical thing is not the central estimate but the coverage probability, i.e. the probability that confidence intervals contain the true value. The probability that the $100(1-\alpha)\%$ confidence interval around Z, namely $(Z-\sigma N_{1-\alpha/2}, Z+\sigma N_{1-\alpha/2})$, will still contain the true value Z_0 is:

$$\frac{\Phi(N_{1-\alpha/2})-\max[\Phi(N_{1-p}),\Phi(-N_{1-\alpha/2})]}{1-\Phi(N_{1-p})} = \frac{1-\alpha/2-\max[1-p,\alpha/2]}{p}$$

$$= \begin{cases} (1-\alpha)/\,p \text{ if } \alpha/2 > 1-p \\ (p-\alpha/2)/\,p \text{ if } \alpha/2 < 1-p \end{cases}$$

In our case, with about 50% power (i.e., $p=0.5$) the statistic (the trend estimate with dose) satisfies $Z > Z_0$, so is likely to be positively biased, i.e., exceed the "true" value by an average of $\sigma\frac{2}{\sqrt{2\pi}} \approx 0.80\sigma$. However, the 95% confidence intervals (i.e., $\alpha=0.05$) will have coverage probability about $(0.5-0.05/2)/0.5=0.95$, i.e., 95% coverage. We judge this to be acceptable.

F1 REFERENCES

Land CE (1980). Estimating cancer risks from low doses of ionizing radiation. *Science* 209(4462): 1197-1203.

Little MP, *et al* (2010). The statistical power of epidemiological studies analyzing the relationship between exposure to ionizing radiation and cancer, with special reference to childhood leukemia and natural background radiation. *Radiation research* 174(3): 387-402.

APPENDIX G Possible biasing effects of gamma ray sampling strategy and measurement error

In considering possible biases in the study the effect of the sampling strategy to measure gamma doses and of random errors in the measurements themselves should be considered. In this context the difference between Classical and Berkson errors is important (Carroll *et al.* 2006). Classical errors are those which arise, for example, because a dosemeter will not give a perfect estimate of the true gamma ray dose rate to which it has been exposed; shortcomings in the instrument will mean that there are random differences between the true quantity and the estimate given by the dosemeter. Berkson errors are those which arise when, for example, group average estimates of radiation exposures are used rather than individual estimates for each study participant. The difference is important because the effect of classical errors is to tend to bias risk estimates towards the null, ie that the estimated risk is likely to be lower than its true value. In contrast, to first order Berkson error results in no bias in the dose response (Carroll *et al* 2006).

There are 4-5 measurement points in each County District (CD) (Wrixon *et al* 1998), and the average of these 4-5 measurements is applied to all persons in the CD. If it were the case that these sampling points were chosen at random from the population, and the measurements in each CD were independent and identically distributed, then this can be easily shown to result in an approximately Berkson error and thus in no bias in the dose response (Carroll *et al* 2006). However, it is known that the measurement sample is likely to be biased: although the original sample of addresses was unbiased, measurements were completed in only 50% of dwellings, with a disproportionate number responding from higher socioeconomic groups. For radon, this is a more serious problem, but for gamma measurements there is no clear socioeconomic gradient. Detached residences have about 10% higher gamma dose rate than flats (Table G1), with semi-detached houses being higher than either, as shown in Table G1.

Table G1 Average dose rate by dwelling type (taken from Wrixon et al (Wrixon *et al* 1998), Table K4)

Dwelling	No. Dwellings	Mean radon (Bq m^{-3})	Mean gamma ray dose rate nGy/h
Detached house	478	21.6	55.3
Semi or terrace	1222	15.8	63.6
Flat or maisonnette	246	13.7	51.4

(Excludes dwellings with Rn concentration more than 2 GSD from the GM)

If we take into account the proportions of persons living in the various types of house (Table G2) one can easily estimate that the mean predicted gamma dose rate given by the NRPB survey would be 59.90 nGy/h, whereas according to the General Household Survey (Office of Population Censuses & Surveys 1984) data it should be 59.87 nGy/h.

Table G2 Percentages of responses by house type in the NRPB survey and nationally. (taken from Wrixon et al (Wrixon *et al* 1998), Table E4)

Dwelling Type	NRPB Survey	General Household Survey
Detached House	25	17
Semi-detached house	39	32
Terraced House	22	32
Purpose-built flat	7	14 (with maisonette)
Maisonette	3	
Other flat, rooms	3	5+
Other	1	1

It therefore appears that the bias in gamma dose rates from this source is negligible.

In addition to the Berkson error resulting from using the averaged dose rate, there may be a component of classical measurement error, resulting from inaccuracies in the gamma dose-rate measurement device. Classical dose measurement error would be expected to result in biasing of trends towards the null, i.e., without correction one would expect to underestimate the true risk (Carroll *et al* 2006). Wrixon et al (Wrixon *et al* 1998) (Appendix C, section C7) state that "NRPB dosemeters were compared with an international standardisation exercise for environmental dosemeters. Agreement between the results of the NRPB dosemeters and the mean of all the dosemeters at each environmental site was generally better than 5%". If the standard deviation of the error in the dosemeter is σ_U, and the standard deviation of the true gamma dose distribution is σ_X, this implies that their ratio is small - probably $\sigma_U / \sigma_X \leq 0.05$. When fitting a linear model the bias in the trend with dose from such a classical dose error model is $\sigma_X{}^2 / [\sigma_X{}^2 + \sigma_U{}^2]$ (Carroll *et al* 2006). As this quantity is within 1% of 1, the bias in the dose response from this source is expected to be minimal.

G1 REFERENCES

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Office of Population Censuses & Surveys (1984). General Household Survey 1982 An Inter-Departmental Survey Sponsered by the Central Statistical Office. London, HMSO.

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