Is indoor radon linked to leukaemia in children and adults? - A review of the evidence

Denis L Henshaw and Janet E Allen

H H Wills Physics Laboratory, University of Bristol, Tyndall Avenue, Bristol, BS8 1TL, UK,
Tel: +44 (0) 117 9260353; Fax: + 44 (0) 117 9251723; e-mail: d.l.henshaw@bris.ac.uk

Abstract

The evidence linking indoor radon exposure to childhood and adult leukaemia is reviewed. At the UK average indoor exposure of 20 Bq m^{-3}, it is estimated that the radon derived equivalent dose accrued to the fetus is 106 μSv. The equivalent dose rate to adult bone marrow ~130 μSv y^{-1}. Standard radiation risk factors suggest that 5% of childhood and 4% of adult leukaemia is linked to radon at 20 Bq m^{-3} exposure. Geographical studies generally support such a link at about this magnitude. A number of case-control studies have been carried out but these in general have not had enough resolving power to determine a link between radon and leukaemia at the level suggested by radiation risk factors.

1. Introduction

Radon causes lung cancer in uranium miners and for many years this was the only clear example that exposure to natural radiation can lead to cancer in humans. There is now strong evidence that radon may cause lung cancer in the general population at elevated levels indoors, but whether this occurs at average domestic levels remains unproven. Information on the risk of childhood leukaemia following exposure to ionising radiation comes from a number of sources, notably the Japanese atomic bomb survivors (BEIR V 1990). Risk assessment based on extrapolation of the Japanese data, suggests that a measurable proportion of childhood leukaemia in the population may be attributed to background radiation. If this is the case then we have reason to assume that radon and its decay products will also cause leukaemia. Radon and its decay products however may be especially important since they emit high LET alpha-radiation. Such radiation (alpha-particles) has been shown to induce both genomic instability and bystander effects in haemopoietic stem cells.

This paper will discuss the arguments that a link between radon and both childhood and adult leukaemia is expected on grounds of risk assessment and will review the attempts to establish whether such a link exists in practice. An earlier review has been given by Little (1999) and a detailed discussion may be found in BEIR VI (1999), chapter 4.

2. Radon derived radiation dose to bone marrow

In radiation dosimetry, considerable effort has been made to model the radon derived dose to the lung and the risk of lung cancer (BEIR VI, 1999). Here the dose arises primarily from the inhalation of the alpha-emitting decay products, ^{218}Po and ^{214}Po which exist in air in aerosol form (figure 1). For leukaemogenesis the target cells are the haemopoietic stem cells which originate in the yolk sac and colonise the bone marrow during fetal development. In this case we need to consider both the behaviour of ^{222}Rn in its own right as well as that of its decay products. We also need to take account of ^{220}Rn (thoron) due to the comparatively long half-life of the decay product ^{212}Pb, 10.6 h, decaying to the alpha-emitter ^{212}Po. In contrast to the lung we are not interested in the details of the tracheo-bronchial deposition of inhaled radon decay products, rather we are interested in their transport around the body once they have entered the bloodstream (Pohl and Pohl-Rühling, 1967.)

When inhaled, ^{222}Rn itself is distributed around the body according to its solubility. The solubility in blood is 0.41 but in body fat it is 16 times greater at 6.3 (Nussbaum and Hursch 1958). Following birth, fat progressively ingrows in bone marrow in the form of fat cells up to 100 μm diameter (Allen *et al* 1995). Radon therefore dissolves preferentially in fat allowing a proportion of the alpha-particle energy from the

decay of radon and its decay products to be deposited in the surrounding haemopoietic tissue. At Bristol we have carried out detailed modelling of the radon and thoron derived dose to the fetus, the child and adult. The fetal dose is particularly relevant because many if not all cases of childhood leukaemia (acute lymphoblastic leukaemia, ALL) are thought to be initiated *in utero* (Ford *et al* 1993, 1997; Gale *et al* 1998; Weimels *et al* 1999).

Figure 2 shows a histological section of fetal bone marrow taken at 35 weeks gestation. The structure of marrow spaces is unlike that in the adult and there is a complete absence of fat cells. By about 14 weeks gestation, the evolving marrow contains haemopoietic stem cells. The number density and spatial distribution of these cells in human fetal bone marrow has recently been mapped (Allen and Henshaw, 2001). Figure 3 shows a schematic diagram illustrating the natural alpha-particle irradiation of fetal bone marrow. The main contributions to radiation dose are from radon and its decay products in bone and

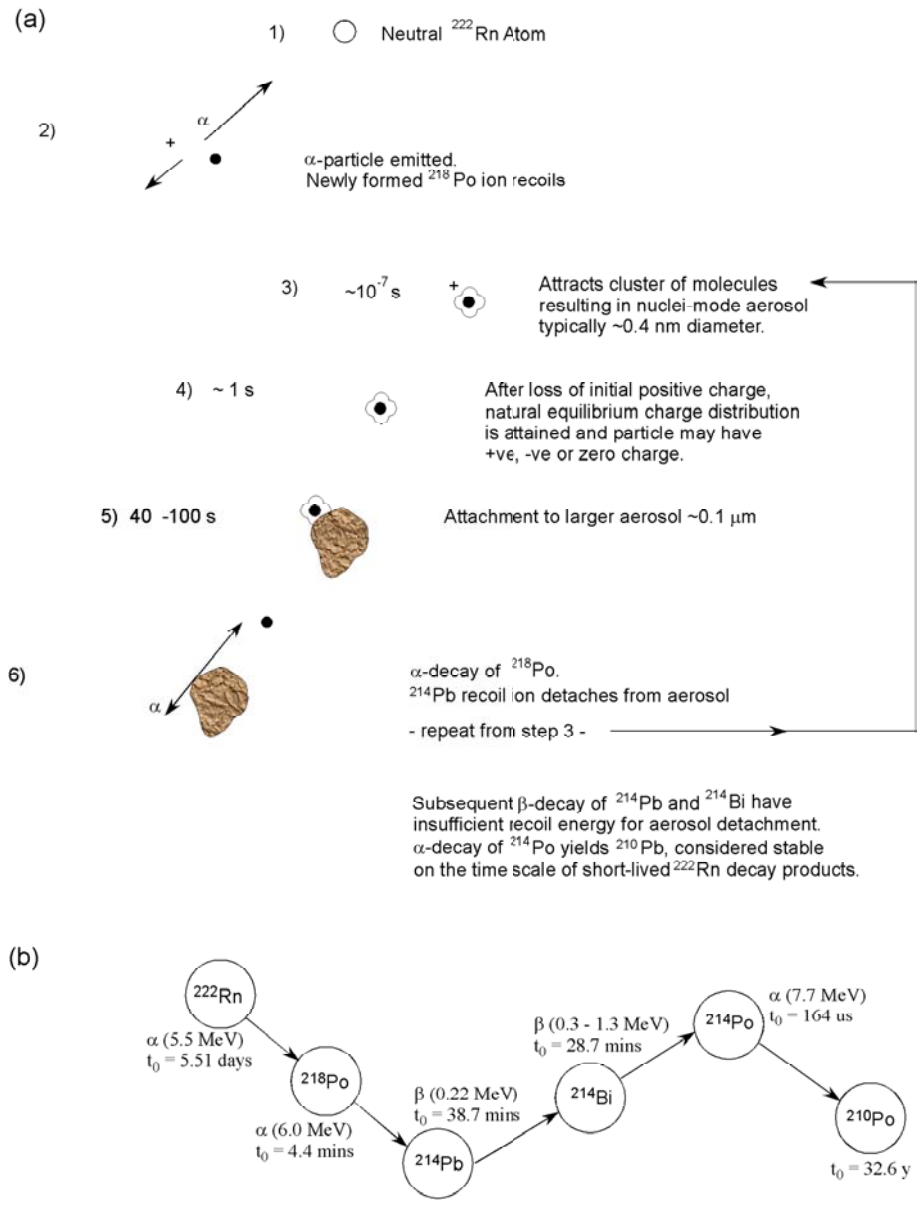

Figure 1. (a) Growth of ^{222}Rn decay product aerosols (b) ^{222}Rn short-lived radionuclide decay chain

marrow and from ^{210}Po emissions in bone. Table 1 shows estimates of the equivalent dose to fetal bone marrow during gestation at various radon concentrations. The accrued dose *in utero* at mean radon exposures of 20, 42 and 1,000 Bq m^{-3} is respectively 106, 150 and 1960 μSv.

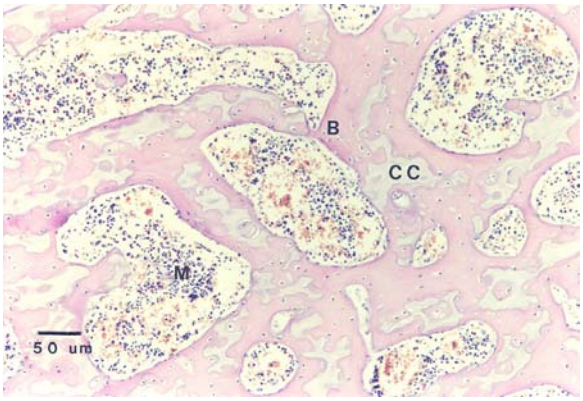

Figure 2. Fetal bone marrow in lumbar vertebra at 35 weeks gestation. B, bone; M, marrow; CC, calcified cartilage.

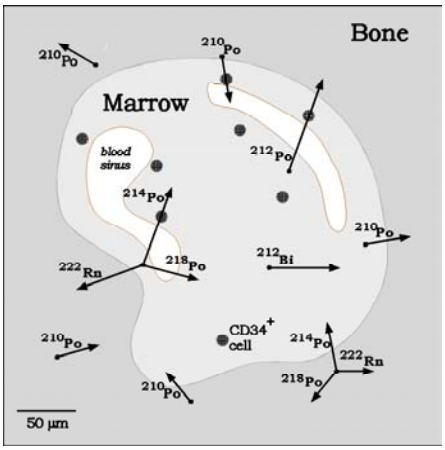

Figure 3. Schematic diagram to show possible paths of alpha-particles from the decay of naturally-occurring alpha-radionuclides.

In adults, a detailed analysis was carried out by Richardson *et al* (1991). The age dependent equivalent dose from radon and its decay products is given in figure 4. In the neonatal period the dose rate is relatively small but in childhood it rises rapidly reaching a peak at age six. These features reflect the age dependent variation in the deposition of inhaled radionuclides taking account of lung development in early years. From age 20 onwards the increasing dose rate is due to the continued ingrowth of fat in marrow (Allen *et al* 1995). The presence of fat cells in marrow is illustrated in figure 5 which shows a histological section of bone marrow from a lumbar vertebra of an 81-year old female caucasian.

Table 1. Radon and thoron derived equivalent dose to the human fetus at three representative indoor levels: 20 Bq m^{-3} (UK average); 42 Bq m^{-3} (world average) and 1,000 Bq m^{-3}.

Radionuclide	**Dose, μSv At**			**Comment**
	20 Bq m^{-3}	**42 Bq m^{-3}**	**1000 Bq m^{-3}**	
Pure ^{222}Rn	12	25	600	Fat free marrow
^{222}Rn decay products	1	2	50	No transfer of bismuth
^{220}Rn decay products	23	48	1150	Transfer of ^{212}Pb
^{210}Po in fetal skeleton (Henshaw *et al*, 1994)	70	75	160	Measured at 20 Bq m^{-3}, scaled for higher exposures
Total	106	150	1960	

The above analysis concerns equivalent dose rate to haemopoietic tissue as a whole. Microdosimetric considerations suggest that a high LET alpha-particle traversing a stem cell deposits around 0.5 Gy of energy resulting in qualitatively different damage to that from low LET (gamma and beta) radiation (Goodhead 1988) and leading to around a 10% chance of cell survival. The recent evidence concerning genomic instability and the bystander effect in haemopoietic stem cells suggests that single alpha-particle traversals through cells may have a much greater effect in introducing cell damage at environmental exposures than

has hitherto been assumed (Kadhim *et al* 1992, Mothersill and Seymour 1998, Prise *et al* 1998, Wright 1998). This is particularly important in the fetus where only a few cells receive alpha-particle hits during gestation.

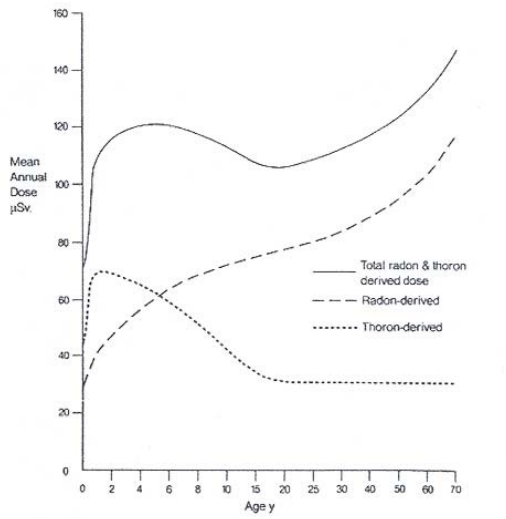

Figure 4. Estimated mean values for the equivalent dose rate to haemopoietic marrow estimated from birth to 70 years old, at 20 Bq m^{-3} radon exposure.

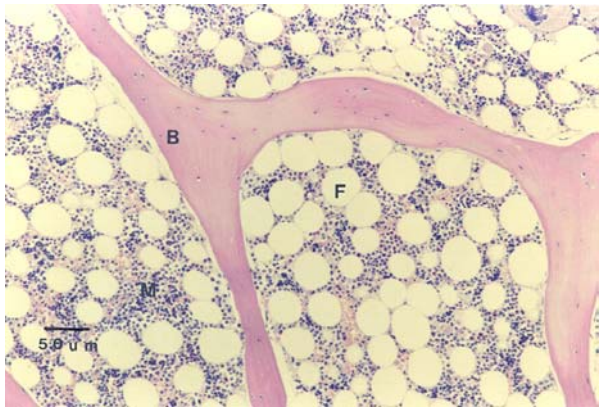

Figure 5. Adult bone marrow in lumbar vertebra of an 81 year old female caucasian.

3. Initial findings

Lucie (1989) reported a statistically significant geographical association in Great Britain between domestic radon exposure and the incidence of acute myeloid leukaemia in adults. No association with gamma radiation was found. Henshaw *et al* (1990) extended this approach and using international data from 14 countries showed a series of correlations between domestic radon exposure, as estimated from national surveys, and the incidence of leukaemia in adults and children. In children, a significant correlation was shown for all cancers combined, for leukaemia and for several specific childhood cancers. In adults, significant correlations were found for acute myeloid leukaemia, AML and for melanoma and kidney cancer. Weak and largely insignificant correlations were found with background gamma radiation. Figure 6 shows a plot of the international data for radon vs. all childhood cancers combined. The gradient of this correlation suggests that if causal, only 6% of all childhood cancer is linked to radon at the UK average indoor radon exposure of 20 Bq m^{-3}. The data in Henshaw *et al* (1990) suggests a percentage link of around 5% and 10% for childhood and adult leukaemia respectively.

There is a further feature of these geographical associations. Henshaw *et al* considered the UK data shown in table 2. For both prostatic cancer and melanoma there is a statistically significant positive correlation with radon, but simultaneously there is a statistically significant negative (anti) correlation with background gamma radiation. A similar though weaker effect is seen for adult and childhood leukaemia. The correlation coefficient between radon and background gamma radiation in the UK is close to zero – i.e. they are uncorrelated. It is generally agreed that geographical correlations should be treated with caution. Why therefore should the effect shown in table 2 occur? Is this a mere artefact, could this be evidence for an antagonistic interaction between radon and gamma radiation, or is it simply mutual confounding of the two radiation types? The dose rate from natural background gamma radiation is such that every stem cell receives one ionising 'hit' per year. On a DNA scale, ionisation from gamma rays is relatively weak and this usually results in DNA single strand breaks (SSBs) which are readily repairable. On the other hand, alpha-particles are highly ionising on a DNA scale with typically 20 ionising events across a 2 nm DNA double strand (Goodhead 1988). This results in a double strand break (DSB) which is difficult or impossible to repair. However, at natural exposures a very small number of stem cells are traversed by an alpha-particle

and in view of the significant differences in LET a mutual (interacting) effect of alpha-particles and gamma rays is thought unlikely (D T Goodhead personal communication). On the other hand, a weak negative correlation with gamma rays could occur by confounding with radon since the variation in gamma ray exposures across the UK is relatively small, whereas for radon far larger variations occur.

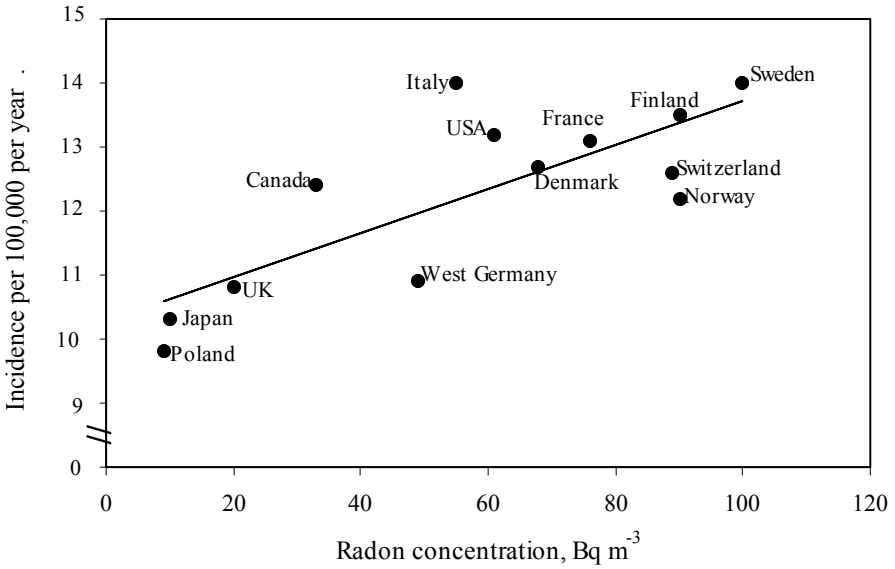

Figure 6. International incidence of all childhood cancers combined vs. radon concentration

4. Leukaemia and radiation risk estimates

Radiation risk factors have been used to estimate the proportion of leukaemia in the population that may be linked to background radiation (COMARE 1996). Overall, 14% of childhood leukaemia has been attributed to natural high LET radiation. When account is taken of the dose to bone marrow from the various naturally occurring alpha-radionuclides (Richardson *et al* 1991, NRPB R276, 1995, table 5.6), 5% of childhood leukaemia and 4% of adult leukaemia may be linked to radon in the UK. Coincidentally therefore the magnitude of the radon-leukaemia link in children derived from risk factors shows agreement with the geographical observations in Henshaw *et al* (1990), but for adults the magnitude of the suggested link is lower.

For childhood/adult leukaemia these risk estimates suggest that for respective domestic radon exposures of 20, 100 and 200 Bq m^{-3}, the relative risk compared to zero radon is around 1.05/1.04, 1.25/1.20 and 1.5/1.4. These values also define the required statistical resolving power for an epidemiological study designed to test the magnitude of this suggested radon link. Thus, epidemiological studies of radon and leukaemia can be seen as an experimental test of the magnitude of the radon/leukaemia link suggested by standard radiation risk factors. Clearly, to be successful such studies must have the requisite resolving power.

5. Assessment of Radon Exposure

The methods of measurement of radon gas concentration are well established and relatively straightforward. Indoor radon levels are known to have substantial diurnal, seasonal and annual variations, and also vary with characteristics of the premises and of lifestyle such as the presence of double glazing and the use of central heating. To determine the mean exposure to radon therefore the preferred method is to use an integrating plastic track detector housed in a small diffusion chamber. For estimations of exposure with respect to the recommended annual limit (200 Bq m^{-3} in the UK), two detectors, one in the bedroom and one in the living area, exposed for three months are considered adequate. For epidemiological studies it would seem essential

that the detectors be exposed for one year. In the studies summarised in tables 3 and 4 below some have measured radon in current as well as previous homes of cases and controls.

Table 2. Radon and gamma correlations for prostatic cancer, melanoma and leukaemia**.**

Data set		Correlation Coefficient		
		Rn	γ-radiation	Rn/γ
Prostate cancer mortality* (54 counties)				
Fractional mortality	AM	0.53 (p<0.001)	-0.49 (p<0.001)	0.73 (p<0.001)
Fractional mortality	GM	0.58 (p<0.001)	-0.55 (p<0.001)	0.83 (p<0.001)
Melanoma mortality* (45 counties)				
Male		0.43 (p<0.01)	-0.55 (p<0.001)	0.63 (p<0.001)
Female		0.41 (p<0.01)	-0.62 (p<0.001)	0.62 (p<0.001)
Leukaemia (Alexander *et al,* 1990)				
Adult AML		0.44 (p<0.05)	-0.27 (ns)	0.46 (p<0.05)
Adult ALL		0.67 (p<0.001)	-0.21 (ns)	-
Childhood ALL		0.65 (p<0.005)	-0.13 (ns)	-
All countries †		0.65 (p<0.02)	0.42 (ns)	0.68 (p<0.01)
5 countries ‡		0.54 (ns)	-0.01 (ns)	0.95 (p<0.01)

* Data courtesy of the MRC Environmental Epidemiology Unit, University of Southampton. Spearman rank correlation coefficients.
† Data from Henshaw *et al,* 1990, Pearson's product moment correlation coefficient, (myeloid leukaemia).
‡Data from Henshaw *et al,* 1990, using only those countries recommended by Butland *et al*, 1990, Pearsons product moment correlation coefficient, (myeloid leukaemia).
AM = Arithmetic mean; GM = Geometric mean; ns = not significant at the 95% confidence level

The measurement of radon gas however may not be an adequate measure of decay product exposure. The ratio of radon decay product concentration in air compared to the radon gas concentration (expressed in terms of the relative concentration of their alpha-particle energies, PAEC) can vary significantly, as can the fraction of decay products which are in small ion form and are unattached to aerosols (the so-called *unattached* fraction). In the case of lung dosimetry, Yu *et al* (2001) have addressed this problem by designing a detector which estimates the bronchial dose from radon decay products in air. In principle this could also be used to estimate bone marrow dose. An additional consideration for bone marrow dosimetry is the thoron concentration in room air. This is not currently estimated in leukaemia studies.

A number of studies have estimated radon exposure in the homes of leukaemia cases from measurements in neighbourhood houses (in the UK, the average radon concentration by postcode). On such a small scale such an estimate is unreliable as may be illustrated in figure 7. This shows how radon concentrations may vary from less than 100 to over 1200 Bq m^{-3} in a row of identically built houses. Other studies have used local geological features to estimate radon exposure of leukaemia cases, notably the study by Kohli *et al* (2000). Friis *et al* (1999) has found evidence that ground level radon is a poor indicator of indoor radon. However, Kohli *et al* have used ground level radon as a measure of temporal exposure to radon and have found a significant association with childhood leukaemia. This study is discussed in more detail below.

6. Epidemiological studies of radon and leukaemia

Table 3 shows the main geographical studies of radon and leukaemia. They are listed in chronological order and include studies in both adults and children. Of the 15 studies, 10 support a link between radon and leukaemia, two studies have suggestive support (Forastiere *et al* 1992, Cohen 1993) and 3 offer no support.

For those with suggestive support, Cohen (1993) found a link between radon and leukaemia in women but not men in the USA, but he also found significant correlations with several cancer sites other than lung in both men and women. For those studies offering no support, Muirhead *et al* (1992a & 1992b) found a positive correlation with radon and a negative correlation with both indoor and outdoor gamma dose rate at county level in Great Britain but the sign of these correlations became reversed when considered at district level within counties. This could be indicative of mutual confounding of radon and gamma radiation. Richardson *et al* (1995) used the same data set and a Bayesian analysis and found a significant correlation for cases occurring in one time period but not for other time periods. Thorne et al (1996) estimated radon exposure by post-code in Devon and Cornwall. Figure 7 shows that radon level by postcode is an unreliable measure of exposure in an individual case. High radon areas are known to be patchy in Southwest England.

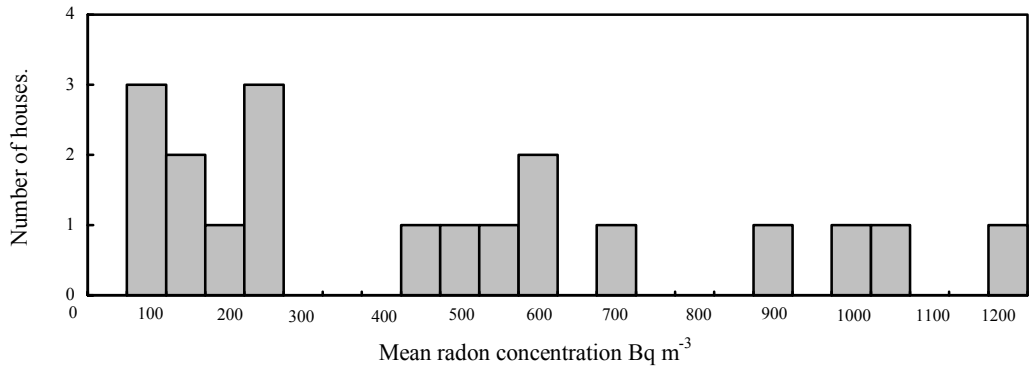

Figure 7. Variation in radon levels in a road of 19 similarly constructed houses in Street, Somerset.

In the studies by Henshaw *et al* (1990), international data was used to obtain good statistics in terms of number of cases and to minimise the effects of small scale geographical variations in radon. Nevertheless, the majority of studies in table 3 do support a link between radon and leukaemia. For the studies in England and Wales, Alexander *et al* (1990) and Lucie (1990) report anomalous effects in the high radon counties of Somerset, Devon and Cornwall. Here the effects of radon and gamma radiation may be hard to separate. In the granite areas of Cornwall radon and gamma levels are both high, whereas in the porous limestone areas of Somerset radon is high but gamma radiation is comparatively low.

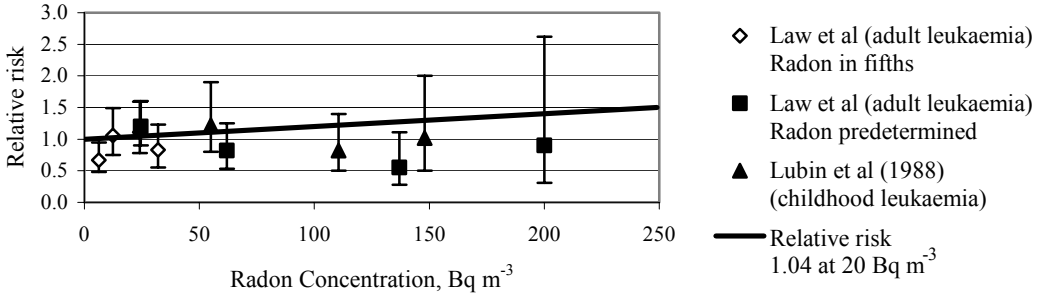

Figure 8. Relative risk of leukaemia with increasing radon concentration

Table 4 lists the main case-control studies of radon and leukaemia. The study by Pobel and Viel (1997) found a statistically significant association between houses made of granite and granite areas and leukaemia in young people <25 years. For the remainder, none has sufficient resolving power to detect a link between radon and leukaemia at the level suggested by radiation risk factors. This is illustrated in figure 8 for the data of Lubin *et al* (1998) and Law *et al* (2000). What these studies do indicate is that in countries such as the UK, where domestic exposure is relatively low, radon poses at most a small public health risk for leukaemia. Additional data is expected to be available from the UK Childhood Cancer Study which is due to publish its results during 2001 for radon and background gamma radiation.

Table 3. Main geographical studies of radon and leukaemia

Author	Study area / Time period	Population	Exposure Assessment	Results
Lucie, 1989	Great Britain Unspecified years	Adults	UK NRPB radon survey	Correlation with AML ($r = 0.48$, $p<0.05$)
Henshaw *et al*, 1990	14 countries 1978 – 1982	Adults and children	Population weighted mean radon exposure from national surveys	Adults: significant correlation for AML. Additional correlation for melanoma and kidney cancer. Childhood cancers: significant correlation for all cancers combined, leukaemia and certain specific cancers.
Alexander *et al*, 1990	England and Wales 1984 – 1988	Adults and children	UK NRPB radon survey	Strong correlation for several haemopoietic disorders especially AML in both adults and children.
Butland *et al*, 1990	Re-analysis of UK data in Henshaw *et al,* 1990	"	"	A significant correlation for childhood leukaemia remains. Other correlations in Henshaw *et al* are largely confirmed, but many fall below statistical significance.
Lucie, 1990	England and Wales 1984 – 1986	Adults and children	"	Correlation with childhood ALL, $r = 0.56$, $p<0.01$. Weaker leukaemia correlations in adults.
Muirhead *et al*, 1991; 1992	England and Wales 1969 – 1983	"	"	Significant positive correlations with childhood leukaemia at county level, but a negative correlation for districts within counties.
Cohen, 1993	USA unspecified years	Adults	US county radon measurements	Correlation with leukaemia in women but not in men. Significant correlation for several other non-lung cancer sites.
Richardson *et al*, 1995	Great Britain 1969 – 1983	Children	"	Significant correlation for ALL for time period 1974 – 1978, not found for other time periods.
Lyman *et al,* 1986	Florida, USA 1981	Adults	Radium in groundwater used as a surrogate for radon exposure	Correlation with radium in groundwater: (1) total leukaemia, $r = 0.56$ ($p<0.01$) (2) AML, $r = 0.45$ ($p<0.05$) High vs. low radium, RR = 2.0

Table 3. (cont'd)

Author	Study area / Time period	Population	Exposure assessment	Results
Collman *et al,* 1991	North Carolina, USA 1950 – 1979	Children	Radon in groundwater used as a measure of domestic exposure.	High vs. low radon: all cancers RR = 1.23 (95% CI = 1.11 – 1.37) leukaemia RR = 1.33 (95% CI = 1.13 – 1.57)
Viel, 1993	France, 41 administrative areas 1984 – 1986	Adults	French national survey	Correlation with AML, for upper and lower tertiles: (1) univariate analysis OR = 1.11 (95% CI = 1.00 – 1.24) (2) multivariate analysis OR + 1.41 (95% CI = 1.25 – 1.62)
Forastiere *et al,* 1992	Viterbo, Italy 1980 - 1986	Adult men 1579 cases 110 mortality cases were lymphatic and haemopoietic conditions	Geological features used to assess indoor radon levels	Excess myeloid leukaemias of borderline significance: high vs. low radon, OR = 2.3, (95% CI = 0.9 – 6.1). Significant OR for kidney cancer, increase for melamona of borderline significance
Hoffman *et al,* 1993	Ellweiler, Germany 1970 - 1989	Children	High concentrations of uranium in sub-soil	7 cases of childhood leukaemia vs 2.3 expected
Thorne *et al,* 1996	Devon and Cornwall, UK. 1976 – 1985	Children 301 cancer cases	Radon exposure estimated by postcode	Non-significant excess for AML. Significant excess for neuroblastoma.
Kohli *et al,* 2000	Östergötland, Sweden 1979 – 1995	Children 53,146 cancer cases	Ground level radon used as a surrogate for indoor radon exposure	For high radon, RR = 5.67 (95% CI = 1.06 – 43) For medium vs. low radon, RR = 4.64 (95% CI = 1.29-28.26). Stronger association with continued residence in high risk area.

Table 4. Main case-control studies of radon and leukaemia

Author	Study area / time period	Population	No. of cases / controls	Exposure assessment	Results
Stjernfeldt *et al,* 1987	Östergötland, Sweden 1980 – 1984	Children	28 / 28	For 15 cases, radon measurements in current and previous homes; for remaining cases only current home measured.	No association with radon
Wakefield and Kohler, 1991	Wessex, UK 1988 – 1991	Children	42 / 39	2 x 3 month radon measurement *	No association with radon
Pobel and Viel, 1997	La Hague, France 1978 – 1993	Young people <25 years	27 / 192	Houses made of granite, used as surrogate radon exposure	RR = 1.18 (95% CI = 1.03 – 1.42)
Lubin *et al,* 1998	9 mid-western or mid-atlantic US states 1989 – 1993	Children	638 / 620	2 × 1 year radon measurement	No consistent association
Forastiere *et al,* 1998	Central Italy 1980 – 1989	Adults	44 / 211	1 × 6 month radon measurement	OR = 0.56 (95% CI = 0.2 – 1.4)
Law *et al,* 2000	UK 1991 – 1996	Adults	578 / 983	2 × 6 month radon measurement	No association with radon

Note: In none of these situations was there sufficient resolution to detect the kind of effect predicted by standard radiation risk factors.

* 2 x 3 denotes 2 radon detectors in the home for three months

Finally the Swedish study by Kohli *et al* (2000) shown in table 3 warrants special mention. The authors carried out a temporal analysis of childhood leukaemia in different areas, assessing radon exposure from the Swedish geological survey office risk classification. The authors found evidence that children born and continuously living in areas classified as high and normal risk from radon have a higher incidence of ALL. They found a stronger association with continued residence at a higher risk area than with place of birth. For the 53,146 cases of childhood malignancy, SMRs for ALL among children born in high, normal and low risk areas were 1.43, 1.17 and 0.25 respectively. The relative risk for the normal and high risk group as compared with the low risk group was 4.64 (95% CI 1.29 – 28.26) and 5.67 (95% CI 1.06 – 42.27). The authors argue that although theirs was a geographical study, it was not based upon aggregated data but thorough individual information. They further argue that ground radon is a better temporal measure of total exposure than after-the-event radon measurements in the home. Notwithstanding the findings of Friis *et al* (1999) which concerned the relationship between contemporaneous ground and indoor radon, we have sympathy with this view. As indicated earlier there is strong evidence that the initiating step in childhood leukaemia is present at birth. Apart from possible genetic factors, this emphasises the importance of *in utero* exposure and therefore the movements of the expectant mother. After-the-event radon measurements in the home may not adequately describe exposure conditions during initiation and progression of childhood leukaemia.

7. Discussion and Conclusion

Geographical studies show a degree of consistency of support for a link between radon and leukaemia in both adults and children at about the level predicted from standard radiation risk factors. Geographical studies it is generally agreed should be treated with caution. A number of case-control studies of radon and leukaemia have been carried of which one has reported a link with radon when granite is used as a surrogate for exposure. Other studies have reported no link but none of these had sufficient resolving power to detect the excess risk suggested by the radiation risk factors. A study by Kohli *et al* (2000) shows a strong association between radon and childhood leukaemia especially with continued residence in areas of high radon risk. Although this was a geographical study, it was not based upon aggregated data but thorough individual information. The authors argue that ground radon is a better temporal measure of total exposure than after-the-event radon measurements in the home.

Further studies of radon and leukaemia are warranted both to test the predictions of radiation risk analysis and to help determine whether the phenomena of genomic instability and the bystander effect impact on risk at natural exposures to high LET radiation. They are also warranted in view of the public health implications in areas and countries with high radon exposures. Future studies must address resolving power and the question of how best to assess exposure to radon, thoron, their decay products and gamma radiation at the time of initiation and progression of leukaemia.

Acknowledgements

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