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Editorial

Radon and Childhood Cancers

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RADON GAS IS A CARCINOGEN

IT IS generally accepted that exposure to high levels of radon gas can cause lung cancer and as a consequence radon gas is classified as a Class I carcinogen by the International Agency for Research on Cancer (IARC) [1]. Evidence to support this is based almost entirely on the experiences of miners of uranium and other minerals who, as a group, are exposed to high concentrations of the gas. Radon exposure is ubiquitous and makes by far the largest single contribution to the dose of natural and man-made ionising radiation which we all receive. However, the radiation emitted by radon and the daughter products into which it decays is predominantly high linear energy transfer (LET) alpha radiation and the degree of biological damage it causes is greater than that of penetrating low LET radiation (e.g. X-ray and gamma radiation). For any given absorbed dose of radiation, the relative biological effectiveness (RBE) of alpha radiation as emitted by radon and its daughters is twenty times that of X-ray and gamma radiation. This RBE factor is taken into account when estimating the equivalent dose from exposure to radon and is measured in units of sieverts. Alpha particles (He^4 nuclei) travel only a short distance in tissue and so the external radiation dose from radon is biologically unimportant—apart from a possible dose to the superficial dermis. The principal biologically active dose from radon and its daughters is the internal radiation dose, the bulk of which is received by the bronchial epithelium as the inhaled particles containing radon and its daughters lodge there. There is little evidence that the radiation emitted by radon and its daughters can effectively deliver a radiation dose to anywhere in the body except the respiratory tract, and the evidence from the miners supports this. Despite prolonged and intense exposures to radon, no consistent excess risk for cancers other than of the respiratory tract has been observed [2, 3] The U.K. National Radiological Protection Board (NRPB) estimate that the dose to red bone marrow from radon is less than one per cent of that delivered to the lung, and that delivered to the bone surface one ten-thousandth of the lung dose [4].

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ENVIRONMENTAL RADON AS A CARCINOGEN

In Devon and Cornwall, where radon levels are up to ten times higher than those elsewhere in the U.K [5], it contributes over 70% of the background radiation dose received, and the radiation dose from radon and its progeny can quite easily approach an effective dose of 9 or 10 mSv per year, but even at this high level of radon concentration, it has not been established, unequivocally, that the risk of lung cancer (or of any cancer) is increased in those so exposed. Lung cancer is a cancer in which 80% of cases are the consequence of known exposure to environmental carcinogens (the primary one being, of course, tobacco smoke). The latency period for the development of lung cancer following these exposures is long, being usually measured in at least years and often decades. This long latency period and the fact that the vast majority of lung cancers are the result of cigarette smoking make the contribution of atmospheric radon to the incidence rate of lung cancer in the general population difficult to measure. Long term exposures to radon are difficult to estimate with any degree of accuracy—especially when individuals tend to move around—and smoking histories are difficult and expensive to obtain. However, it has been estimated that, in the United States, radon may be responsible for 12% of all lung cancer deaths, which implies an additional 15000 deaths from lung cancer per year—10000 in smokers (9% of all such deaths) and 5000 in never smokers (30% of such deaths) [6]. Dr Sarah Derby and her colleagues at Oxford, with the help of the U.K. Office of Population Censuses and Surveys, are currently conducting a difficult study of long term radon exposure and lung cancer in South-West England, and the results of this study will no doubt provide valuable evidence of the radon related risk of lung cancer in that population.

'Population correlation' or 'ecological studies' by Henshaw and his colleagues [7] have suggested that the incidence rate of several other cancers in the general population, for example acute myeloid leukaemia and malignant melanoma, are correlated with radon levels and that these correlations may reflect a causal association. However, the findings of these studies are difficult to interpret and the biological pathway by which these cancers could result from radon exposures, bearing in mind the very low dose to non-respiratory tract tissue, remains uncertain.

RADON AND CHILDHOOD CANCERS

Childhood cancers are aetiologically very different from adult lung cancer. By definition, if there is a causal environmental exposure for childhood cancer, the latent period must be short—months or years but never decades. In addition, many childhood cancers probably have their origins *in utero*, in which case any causal exposures of interest must be considered to act before birth, or in some cases even before conception.

Thorne and his colleagues [8], in this issue (pp. 282–285), present the results of an ecological study where they have examined the rates of cancer in children resident in postcode sectors of 'high' or 'low' radon levels. They have found no difference in rates of childhood cancer as a whole between their two categories of residential exposure and conclude that lifetime exposure to radon gas does not affect the risk of childhood cancer. They have found a significant excess of neuroblastoma in the high dose group, but are cautious in their interpretation of this.

Two questions remain to be addressed in interpreting these conclusions. Firstly, is it biologically plausible that exposure to environmental radon could increase the risk of malignancies in children. Secondly, is the study presented by Thorne and his colleagues sufficiently powerful to be able to detect such an excess, if present?

BIOLOGICAL PLAUSIBILITY OF RADON AS A CAUSE OF CHILDHOOD CANCER

The biological plausibility of radon as a cause of children's cancers relates primarily to the maximum cumulative radiation dose which it would be possible for the children to accrue and what is already known of the excess cancer risk associated with doses of this magnitude, and secondly to the wide spectrum of children's malignancies and what we already know of their aetiology.

Children living in the postcodes of highest radiation exposure, say 180 becquerels of radioactivity per cubic metre, will be exposed to an effective dose of some 11 mSv of radiation per year background radiation from all sources including a radiation dose from radon of 9 mSv (Figure 1).

Lifetime exposure to radon at a concentration of 200 becquerels per cubic metre is equivalent to an excess lifetime risk of lung cancer of around 3 per 100. Hence, the risk of lung cancer from exposure to radon in the areas of Devon and Cornwall, where it is highest, is substantial. The magnitude of the childhood exposures over a 15 year span are comparable to the lower ranges of those which have been found in the studies of miners to be associated with an excess of lung cancer.

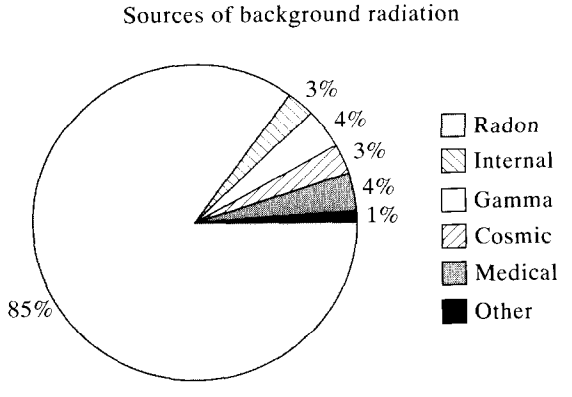

Figure 1. The relative contribution from all sources to the annual effective radiation dose to residents in areas of radon concentration 180 becquerels per cubic metre are shown. The average radiation dose is 10.6 mSv per year.

By the age of 15, children could have been exposed to effective radiation doses of around 150 mSv. These childhood doses are comparable to those arising from occupational exposure to predominantly low LET radiation in the nuclear industry and which are associated with a risk of leukaemia [9]. However, whilst these exposures are of a similar magnitude, the dose to the children from radon is confined almost entirely to the bronchial epithelium. Children exposed to radiation during treatment with radiotherapy are known to be at increased risk of second malignancies, although the exposures in these groups are high (average dose of 27 Sv in 54 observed cases of bone and connective tissue cancer) and the excess relative risk at 0.06 (0.01–0.2) per Sv for bone and connective tissue cancer is low [3]. Exposures of around 100 mSv were experienced in children given radiotherapy for tinea capitis, and in these children an excess relative risk per Sv of thyroid cancer of 7.7–34 was observed [3]. This study also showed, as others have done, that the risk for specific cancers for any dose of radiation is much greater when exposure is at a younger age. It is, therefore, plausible that radon exposures at the high levels found in Devon and Cornwall, especially in very young children, could be associated with an excess of paediatric malignancies.

That only respiratory tract cancers have been attributed to radon in miners does not neccessarily preclude an effect in children—there is consistent evidence that exposure at a younger age is much more damaging, as is dose accumulated slowly. The children could well be more sensitive to the small whole body radiation dose resulting from their radon exposure. Alternatively, it has been suggested that, as a consequence of the mining activity, the effect of radon on the miners is greater than would be expected from a similar domestic exposure.

The fetus *in utero* is at particular risk of damage from radiation. However, the radiation dose to the fetus from inhaled radon is probably very small. Uranium-bearing rock is a source of both gamma radiation and radon gas. However, the radon gas only escapes into the atmosphere if the rock is fissured and so it is possible to have areas of high gamma radiation with or without a corresponding elevation in radon levels. However, it should be noted, that indoor gamma radiation in Cornwall in particular is two or three times higher than the average for the rest of the British Isles, and it may be that gamma radiation contributes the greater proportion of the fetal radiation dose. Richardson and her colleagues have failed to find any consistent association between childhood leukaemia, which accounts for around one third of all childhood malignancies, and either background gamma radiation or radon levels [10], even though it is known that irradiation *in utero* and in childhood increases the risk of leukaemia.

POPULATION CORRELATION STUDIES OF CHILDHOOD CANCER IN SOUTH-WEST ENGLAND

The second question concerns whether the study by Thorne and colleagues reported in this issue (pp. 282–285) is of sufficient power and specificity to address the hypothesis of radon exposure and childhood cancer risk.

As with any population correlation study, it relies upon grouping populations from a large geographical area, and in this case time period, and allocating an 'average' attribute to this population (in this case radon dose). Parts of each population group will have been incorrectly ascribed the exposure characteristic. As with any population variable, many individuals will have values of that characteristic which are towards the top end or the bottom end of the range. Radon levels can vary enormously even over small areas—for example adjacent houses can have very different concentrations (perhaps a 4-fold difference) of radon depending on both the construction of the house and its ventilation.

When divided into postcode areas of 'high' and 'low' radon, there will inevitably be some misclassification of households—some will be in a 'high' radon postcode, but will actually have levels which fall into the 'low' range and vice versa. The advantages of population correlation studies are best exploited when very large data sets are compared—for example at national level—and the exposure characteristics of the discrete populations are very different. On this very large scale, it may be possible to detect small differences in risk which would be difficult to measure in smaller samples. However, even when very large populations are considered, there is still always the concern that in diseases such as cancer, which have multiple causes, the interpretation of a positive correlation between disease risk and exposure level of one risk factor as a causal association is too simplistic an approach.

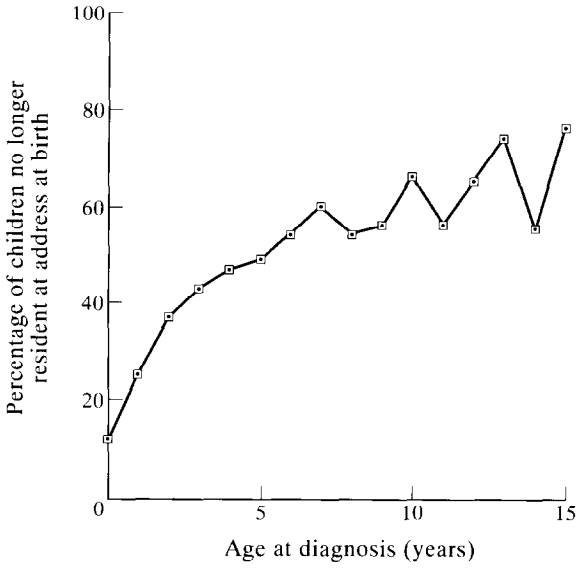

Figure 2. Percentage of children registered with the Northern Region Young Persons Malignant Disease Register (1968–1985) who moved house between birth and diagnosis by age of diagnosis.

SOURCES OF MISCLASSIFICATION

In the study presented in this issue, the geographical areas used in the comparison are fairly small, being of the order of counties and the outcome, children's cancer, is a rare condition. The necessary restriction on both the numerator and denominators constructed for the comparison limit the power of the study to detect small differences in disease risk. In addition, the assignment of radon dose to postcode areas is an approximation.

The radon level within households will also have changed dramatically over the course of the study. For example, radon levels in the 1970s would have been much lower than in the 1980s because of trends in housing—such as fitting double-glazing and abandoning chimneys—which have increased interior radon levels. This misclassification will bias the findings towards the null, i.e. would make 'true' association more difficult to find.

In assuming that the exposure of interest is related to the residential address at diagnosis, a second misclassification is introduced. By the age of 15 years, up to 70% of the children will have moved house between birth and diagnosis (Figure 2; previously unpublished data). Even though many of these moves will be of a short distance, they may well be between postcodes which fall into different radon dose categories. Any effect of radon exposure would be anticipated to have a latency period and it may well be that, for any individual, the period of important exposure was at a previous address or even occurred before or around the time of birth, which is, by implication, likely to be the time of greatest sensitivity to radiation. Hence, for a proportion of the children with cancer, the characteristics of the address of diagnosis will be completely irrelevant. Many childhood malignancies affect very young children. The vast majority of children with the most common solid tumour of childhood, neuroblastoma, for example, are diagnosed before their fifth birthday; acute lymphoblastic leukaemia is most common in children aged 2–5 years. It is likely that any important environmental exposure to carcinogens would have to occur early in life, or even before birth. The address of relevance may therefore be that of birth and not of diagnosis. Thorne and colleagues noted a significant excess of risk of neuroblastoma in the high radon postcode group. If this proves to be a replicable finding, it could imply that, since neuroblastoma is a disease of young children which is considered largely to be present from birth, that it is exposure at and around birth which is important. In this young group, fewer will have moved house and so for a larger proportion the address at diagnosis will be the same as that of birth and hence will still be relevant. However, the incidence rate of neuroblastoma in the high dose group (12 per million per year) was not dissimilar to that of the rest of the U.K. (9–10 per million per year), suggesting that the apparently low rate in the 'low' dose group may be a chance occurrence. Indeed, it is known from studies published elsewhere that the reported rate of childhood cancer in the South-West is little different to that elsewhere in the U.K. [11].

Another potential source of misclassification is in the allocation of population to postcode areas. There have been major demographic changes in the population of Devon and Cornwall over the period during which the study children were drawn, a 3% shift in overall population between 1971 and 1981 censuses masks what may have been substantial exchange in population between 'high' and 'low' dose postcode areas.

Devon and Cornwall are both counties which have amongst the highest levels of radon in the U.K. Even houses correctly allocated to the 'low' dose group will have some of the highest

radon levels in the country. The contrast, therefore, between the exposures of the high dose group and the low dose group is not as extreme as it would be if the low dose group was geographically more remote.

Despite the apparently large number of person years in the study groups, misclassifications of population and cases between high and low dose groups will inevitably have diminished its power in detecting small effects. With no misclassification, the study is a comparison of two populations, with annual effective radiation doses from radon of 9 and 5 mSv. However, with misclassification of populations between groups of 30% (for the reasons given above), which is not an unreasonable estimate, the study is comparing the effects of annual doses of 7.8 and 6.2 mSv, respectively, a difference which would not be detectable in a study such as this.

SUMMARY

The effective radiation doses received by children living in high radon areas are similar to those which have been associated with an excess risk of malignant disease elsewhere. However, the only cancer known to be associated with radon is lung cancer—a disease which is not a condition of childhood. Thorne and his colleagues have conducted a study which could have demonstrated an excess of childhood malignancy only if the risk associated with radon was very high.

The risk to health of high levels of radon in the environment remains uncertain. The United Kingdom Case Control Study of Childhood Cancers, under the chairmanship of Sir Richard Doll, is assessing risk from many factors including measured radon exposure and it is with great interest that we await the results.

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