Institution: University College London (UCL)

Unit of Assessment: 10 – Mathematical Sciences

Title of case study: Radon exposure: Informing advisory guidelines

1. Summary of the impact (indicative maximum 100 words)

UCL research on statistical methodology has underpinned important investigations by scientists at Oxford University into the relationship between exposure to the naturally occurring radioactive gas radon and lung cancer. The resulting dose-response relationships and risk estimates have informed advice given in 2008-10 to the UK government by the Health Protection Agency about the risk of radon exposure and the cost-effectiveness of radon control policies. They have also influenced the conclusions of the World Health Organization about indoor radon and lung cancer, as reported in their 2009 handbook. Furthermore, the research findings have led to proposals for changes to building regulations in the UK and elsewhere, and changes to the building code in Finland have resulted in a reduction in the average indoor radon concentration in new homes.

2. Underpinning research

Evidence of an association between exposure to radon gas and increased rates of lung cancer has been available for over 100 years, but this early evidence was based on the exposure of uranium miners to very high doses of radon. However, people are also exposed to low doses of radon simply by living in their homes; granite – the underlying rock in many areas – contains low concentrations of the gas, which seeps up through the ground into buildings (the average concentration inside homes is 20 Bq m^{-3}). It is therefore important to estimate the risk of lung cancer associated with these low doses, in order to judge whether and when preventive measures should be taken. In the past, this estimation was done by extrapolating from high to low doses of radon, but about 20 years ago advances in instrumentation for measuring radon concentrations in the home opened up the possibility of direct estimation of the risk of developing lung cancer due to domestic exposure. In the last 20 years, several countries have carried out case-control studies, in which lung cancer patients are matched with a control group and the radon exposure histories of both groups – obtained by retrospective measurements in the homes they have lived in – are compared and, in particular, are used to estimate a dose-response relationship. This requires adjustments for various other factors, of which smoking history is the most important.

Since the early 1990s, Tom Fearn (Senior Lecturer 1989-96; Reader 1996-99; Professor 1999-present) in UCL's Department of Statistical Science has worked closely with a group of scientists in the University of Oxford's Clinical Trials Support Unit (CTSU) on a number of studies relating to radon exposure. The CTSU group has been instrumental in carrying out a large case-control study in the south-west of England [1], and in pooling the results of 13 European case-control studies [2, 3]. This latter exercise did not just combine the published risk estimates, but rather involved an analysis of the pooled data from all of the studies. Fearn's contribution to the work was in providing statistical methodology that underpinned the data analyses in the CTSU group's studies, as well as contributing to the data analysis.

One relatively straightforward contribution from Fearn, with background and data provided by Sarah Darby at CTSU and Jon Miles at the National Radiological Protection Board, was a methodology [4] for applying a seasonal variation correction to domestic radon measurements, which are typically taken by placing a detector in the home for six months. This seasonal variation correction is important because summer measurements of internal radon concentrations are lower than winter ones (due to the release of radon to the outside through open windows), and so a six-month average is not an accurate estimate of the annual dose. The methodology developed at UCL involved smoothing and extrapolation with periodic functions, and was used to correct the dose measurements from the south-west England study [1] that was carried out between 1988 and 1998.

A major difficulty in correctly estimating the dose-response relationship in case-control studies of radon and lung cancer is that there is very substantial measurement error in the radon measurements, with a typical coefficient of variation being 50%. It is well known that error in the x-variable flattens regressions, leading to slope estimates that are too low. Correcting for this effect is a simple matter for linear regression models; however, the model typically used to analyse these case-control studies is a logistic regression of case-control status on dose and covariates (such as smoking), fitted by maximum likelihood, for which the simple correction methods do not apply. In the analysis of the south-west England study [1], an approximate method by Cox and Reeves of Oxford University was used to make the correction. Fearn was closely involved in the implementation of this methodology; for example, advising on the estimation of measurement error variances in the situation where the exposure measurement is a sum over several homes with a proportion of missing data.

For the European pooling study, on which work began in about 2003, this approximate method for correcting for the radon measurement error was considered to be inadequate. The main reason for this was the need to include study-specific adjustment for a substantial number of covariates. With large numbers of covariates maximum likelihood is biased, and it is preferable to implement the analysis using stratification and a conditional logistic likelihood, for which the Cox-Reeves approach does not work. Fearn therefore developed a new methodology based on numerically integrating the conditional logistic likelihood [5], with input on the context from Darby at CTSU and some computing assistance from David Hill at CTSU. This method is exact (if the distributional assumptions are correct), but computationally expensive, and was used in the data analysis reported in the European pooling study [2, 3].

In the case-control [1] and European pooling [2, 3] studies it was found that appropriate correction for radon measurement error using the methods described above roughly doubled the estimate of the slope in the linear (for log odds) dose-response, i.e. the risk of developing lung cancer from exposure to radon was estimated to be twice as great as previously thought. This has important implications for policy decisions, where, for example, cost-benefit analyses of the value of remedial action in buildings need to be based on the correct estimates of risk. The two studies resulted in similar estimates of the risk of lung cancer from exposure to radon, but that from the pooled analysis has the advantage of being both much more precise and more appropriate for international use, because it was based on almost all the international data available at the time. The pooled analysis also found that there was no evidence of a dose threshold (i.e. a radon dose below which there is no effect), which also has important implications for public health policy since there is no dose that can be regarded as safe [2, 3]. A further important finding was that exposure to radon multiplies the risk of lung cancer from smoking, so that those who smoke – or who have smoked in the past – are at much higher absolute risk than lifelong non-smokers.

Note that Fearn is not an author on references [2] and [3], despite contributing substantially to the data analysis, because of a two-per-study limit on authors (his contribution is instead acknowledged on page 53 of reference [2]). Please also note that although the methodology in reference [5] is described in detail in reference [2], the paper is not cited there because it was published later, the large time gap being due to differences in editorial practices between medical and statistical journals.

3. References to the research

[1] Risk of lung cancer associated with residential radon exposure in south-west England: a case-control study, S. Darby, E. Whitley, P. Silcocks, B. Thakrar, M. Green, P. Lomas, J. Miles, G. Reeves, T. Fearn and R. Doll, *British Journal of Cancer*, 78, 394-408 (1998) doi:10.1038/bjc.1998.506

[2] Residential radon and lung cancer—detailed results of a collaborative analysis of individual data on 7,148 subjects with lung cancer and 14,208 subjects without lung cancer from 13 epidemiological studies in Europe, S. Darby, et al., *Scandinavian Journal of Work, Environment and Health*, 32, suppl. 1, 1-84 (2006) http://www.sjweh.fi/show_abstract.php?abstract_id=982

[3] Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies, S. Darby et al., *BMJ*, 330, 223 (2005) doi:10/fkjn77

[4] Seasonal correction factors for indoor radon measurements in the United Kingdom, J. Pinel, T. Fearn, S. C. Darby and J. C. H. Miles, *Radiation Protection Dosimetry*, 58, 127-132 (1995) http://rpd.oxfordjournals.org/content/58/2/127.abstract

[5] Measurement error in the explanatory variable of a binary regression: Regression calibration and integrated conditional likelihood in studies of residential radon and lung cancer, T. Fearn, D. C. Hill and S. C. Darby, *Statistics in Medicine*, 27, 2159-2176 (2008) doi:10.1002/sim.3163

References [5], [4] and [1] best indicate the quality of the underpinning UCL research.

4. Details of the impact

Radon is the single biggest source of public radiation exposure in the UK and is responsible for an estimated 1,100 lung cancer deaths a year [A]. Prior to the case-control studies of domestic radon described in section 2, it was generally thought that radon-related lung cancer occurred mainly in individuals exposed to the gas at very high concentrations. This belief arose because most of the previous evidence of a link between radon exposure and lung cancer came from studies of miners who had been exposed to high doses occupationally. Consequently, guidelines issued by official public health bodies – both nationally and internationally – focused almost entirely on the avoidance of high exposures above certain levels.

The finding of the domestic studies that there is a clearly detectable risk of lung cancer at radon concentrations below the minimum levels for intervention suggests, however, that the majority of radon-related lung cancers occur in people exposed to only moderate concentrations; the risk is low, but in the absence of preventive measures many more people are exposed to the gas at these levels. This research finding therefore has substantial implications for the most appropriate way to reduce the average public exposure to radon, with a shift in emphasis from measurement and remediation in existing homes to the installation of preventive measures – such as thicker and better sealed damp-proof membranes in floors – in large numbers of new homes. This change in emphasis has been highlighted in national and international reports evaluating the public health aspects of radon.

In the UK, the Health Protection Agency (HPA) has, since 2008, provided government with updated advice about the risk of radon, which replaced the previous advice published in 1990 by the National Radiological Protection Board. This updated advice was influenced by the research findings of the European pooling study (references [2] and [3] in section 3) and consisted of recommendations about building regulations made in 2008 [B], followed by further advice in 2010 on limiting public exposure to radon [C]. Recognition that there is a risk of lung cancer from radon concentrations below the UK intervention level (together with other factors) led the HPA to recommend to the Department of Health in the 2008 document that “building regulations and supporting documents should be amended to ensure that all new buildings, extensions, conversions and refurbished buildings in the UK include basic radon protective measures” [B].

This advice was followed in 2009 by a substantial review by the HPA’s independent Advisory Group on Ionising Radiation (AGIR) of the effects of radon on the health of the population [A], which further concluded that changes by government to building regulations have the potential to reduce the total number of deaths due to radon in a cost-effective way. The European pooling study is extensively cited in this document and provided important evidence that helped shape the AGIR’s advice to the HPA; the report states: “The association between the long-term average residential radon concentration and the risk of lung cancer found in a pooled analysis of individual data from 13 European studies is the best current basis for risk estimation” [A]. It goes on to repeat the finding from the European pooling study that there is an estimated 16% increase in lung cancer risk per 100 Bq m^{-3} increase in concentration of radon gas. This estimate was used by the AGIR in a cost-benefit analysis, to evaluate the cost-effectiveness of current and possible future radon control policies for the UK. Amongst other things, this analysis concluded that (1) not only was the current government policy to install radon preventive methods in all new homes in areas with average concentrations above 52 Bq m^{-3} cost-effective; but that (2) extending this requirement to all new homes nationwide would also be cost-effective and would avert considerably more lung cancers (242 in the first 10 years of the policy compared with 28) [A]. In response to the AGIR review, the HPA published its current advice to government in 2010 [C], which reiterates the recommendations of the AGIR and additionally recommends that a new Target Level of 100 Bq m^{-3} should be introduced alongside the current Action Level of 200 Bq m^{-3}. Preventive measures are already required in new homes if the probability of exceeding the Action Level is 1-3%; the Target Level is the concentration above which the HPA recommends householders seriously consider taking remedial action. Having two levels also “avoids the false impression that there is a clear boundary between safe and unsafe radon concentrations” [C]. This 2010 advisory document also states that the European pooling study provides the “best information on the risks from radon exposure in homes” currently available and repeats the findings of that work [C].

Internationally, in 2009 the World Health Organization (WHO) published a handbook on indoor radon [D], designed to aid the development of national radon programmes and to inform stakeholders involved in radon control, such as the construction industry. This handbook also cites the European pooling study extensively, noting that it is the only one of the three existing pooling exercises (this one and two smaller ones involving US and Chinese data respectively) to correct for measurement error; indeed, the authors of the WHO report applied approximate corrections to the risk estimates from the other two studies to bring them into line with the European one [D]. Two conclusions of the WHO that are heavily dependent on the European pooling study are: “The majority of radon-induced lung cancers are caused by low and moderate radon concentrations rather than by high radon concentrations, because in general less people are exposed to high indoor radon concentrations”, and “Radon is much more likely to cause lung cancer in people who smoke...” [D]. The handbook goes on to outline the implications for policy, such as the need to provide protection against low exposures. It also summarises the cost-benefit analysis in the AGIR report and highlights it as a good example of how to use the risk estimates as a scientific basis for policy making [D]. The increase in absolute risk from radon exposure for smokers was also highlighted in the 2010 WHO guidelines on indoor air quality [E], where the different levels of risk according to smoking status were provided and the European pooling study was cited as one of the primary sources of evidence. These guidelines are targeted at public health professionals involved in preventing health risks of environmental exposures, and aim to provide a scientific basis for legally enforceable standards.

The process of moving from reports by committees to changes in legislation is a slow one, but in several countries there is a move towards revising national policy on the control of risks from domestic radon exposure, with a shift from searching for homes with high radon concentrations and remediating them, to the introduction of radon preventive measures in large numbers of homes. For example, Finland, influenced by the south-west England study (reference [1] in section 3) as well as by its own national study, changed its building code in 2004 to require more effective radon preventive measures in new buildings; a survey conducted in 2009 revealed that these improved measures had resulted in a 33% lower average indoor radon concentration in new homes [F]. In Germany there is current discussion, motivated in part by the risk estimates from the European pooling study, on a move in this direction [G], and the UK is also considering changes in light of the cost-benefit study in the AGIR report.

5. Sources to corroborate the impact

[A] Radon and Public Health: Report of the independent Advisory Group on Ionising Radiation (2009), available online: http://bit.ly/1cRj9JF – corroborates the influence of the European pooling study on the advice in the report. Also corroborates the number of estimated deaths and the conclusions and recommendations made. In particular, see pages 21-25, 43-55 and 58.

[B] HPA Advice on Radon Protective Measures in New Buildings (2008), available online: http://bit.ly/187nfK6 – corroborates the influence of the research on the advice, and corroborates the recommendation to government to amend building regulations.

[C] Limitation of Human Exposure to Radon: Advice from the Health Protection Agency (2010), available online: http://bit.ly/1bYjPM9 – corroborates the recommendations made to government, and the influence of the research on the advice. In particular, see pages 7, 8 and 15-18.

[D] WHO Handbook on Indoor Radon: a Public Health Perspective (2009), available online: http://bit.ly/1bbmf8A – corroborates the influence of the research findings on the content and conclusions of the handbook. In particular, see pages 3, 7-16 and 63-69.

[E] WHO Guidelines for Indoor Air Quality (2010), available online: http://bit.ly/1grkUSx – corroborates the influence of the research on the guidelines. In particular, see pages 361-362.

[F] Radon prevention in new construction in Finland: a nationwide sample survey in 2009, H. Arvela, O. Holmgren and H. Reisbacka, *Radiat. Prot. Dosimet.*, 148, 465-474 (2012) doi:10/dz65j2 – corroborates that Finland changed its building code in 2004 and the benefits of this change.

[G] The Working Group Manager at the Institute of Radiation Protection in Germany can be contacted to corroborate that changes to building codes are being discussed in Germany, motivated by the research findings. Contact details provided separately.