

**Radon in homes and lung cancer risk:
collaborative analysis of individual data from
13 European case-control studies**

Additional Methodological Material

Criteria for inclusion in the Collaborative Analysis

European studies of the relationship between residential radon and lung cancer were selected for inclusion in the Collaborative Analysis provided that they satisfied the following criteria: clear rules had been used in the selection of subjects with lung cancer; control subjects had been selected in such a way as to be representative of the population from which the subjects with lung cancer had been drawn; detailed residential histories going back at least 15 years had been compiled in a similar way both for subjects with lung cancer and for control subjects; long term (minimum 2 months) measurements of radon gas concentration that were likely to be representative of the levels experienced by the study subjects during the time they were living there had been made for the majority of residences; data on smoking habits and other variables were available for each subject, collected either from the subject in person or from the subject's next of kin; information on the design of the study was available and on its completeness in relation to the target populations of cases and controls; the study included at least 150 subjects with lung cancer and 150 controls. A total of 13 studies satisfied these criteria, and all were included in the Collaborative Analysis. Twelve studies used a case-control design, while the Czech study used a nested case-control design within a cohort study. Seven studies (England, France, Eastern Germany, Western Germany, Italy, Spain, Stockholm) enrolled lung cancer cases prospectively, while six (Austria, Czech Republic, Finland nationwide, South Finland, Sweden nationwide, Sweden never-smokers) used primarily cancer or death registries. Most studies included both sexes, but the South Finland study included only males and the Stockholm study only females. Most studies included only population-based controls, but three (England, Sweden: never-smokers, and Sweden: Stockholm) included both hospital and population controls and two (France and Italy) included only hospital controls. Four (England, Finland nationwide, France and Italy) included only long term residents of their area.

Method of estimation of residential radon concentration in dwellings where no measurement could be obtained

For dwellings where the radon concentration could not be measured an indirect estimate was constructed, based on the measurements made for the controls in the same study. Ideally,

such estimates would be based on the distribution of radon concentrations in the whole population. In these case-control studies the controls will, to a close approximation, reflect the distribution in the population as a whole. Therefore, the estimates in each study were based on the measurements made for the controls in the same study. These estimates were either the overall arithmetic mean for all the controls or else area-specific control means. For each study, the effect of using area-specific means as compared with the overall mean was evaluated by considering all the available measurements in each study and calculating the mean squared error of prediction using the overall and area-specific estimates. In four studies (Austria, Czech Republic, Italy, United Kingdom), the use of area-specific estimates improved the mean squared error of prediction by more than 10% and area-specific estimates were used throughout the analysis. For the remaining studies, the reduction in the mean squared error of prediction was less than 10% and estimates for missing values were based on the overall mean of measurements made in the controls.

Statistical Methods

Main analyses based on measured radon

The association between radon and lung cancer risk was studied by considering the relationship between the odds of developing lung cancer and various measures of radon exposure using the linear odds model:

$$\frac{\pi}{1-\pi} = e^{\alpha}(1 + \beta x), \quad (1)$$

where π is the probability of developing lung cancer, x is a continuous variable summarizing the radon exposure of each subject, e^{α} is the odds of developing lung cancer when $x=0$, and β describes the linear relationship between the odds of developing lung cancer and radon exposure. This model was used, rather than the usual logistic regression model, because radiobiological theory suggests that it is more appropriate to quantify the risk on a linear rather than on an exponential scale. Also, results expressed on a linear scale are more easily applied in the context of radiological protection.

For most of the initial analyses X was the time-weighted average measured radon concentration for a subject, and was calculated as $X = \sum_j W_j X_j$ where the X_j are the measured radon concentrations (either measured or else estimated indirectly where no measurement could be made) corresponding to the dwellings occupied by the subject during the 30-year period of interest, and the weights W_j are the proportions of the 30-year period of interest corresponding to each dwelling.

As the probability of developing lung cancer is small, $\frac{\pi}{1-\pi} \approx \pi$ in equation (1), and $1+\beta X$ is, to a good approximation, the relative risk of lung cancer when radon exposure takes value X compared with no radon exposure or, equivalently, β is, to a good approximation, the proportionate increase in risk of lung cancer per unit increase in radon exposure.

Allowance was made for potential confounders through stratification [ie by allowing each stratum to have its own α in equation (1)]. Within each stratum, the number of subjects with lung cancer was assumed to have a binomial distribution with parameters N and π , where N is the total number of subjects in the stratum. Models were fitted using conditional maximum likelihood, along the lines usually used in conditional logistic regression. Software packages Epicure¹ and Stata² were used. When linear odds models of the form given in equation (1) were used, confidence intervals for β were based on the conditional likelihood and, as the log likelihood was asymmetric, these usually differed appreciably from those based on standard errors. For some analyses the lower bound of the confidence interval, and occasionally also the estimated value of β , could not be evaluated precisely as it was less than $-1/X_{max}$, where X_{max} was the largest value of X in the data, and thus corresponded to negative fitted values for the odds. In such cases all that could be presented was the fact that the value was less than $-1/X_{max}$.

In analyses exploring the potential heterogeneity of β with various categorical attributes of the subjects, the single term βX was replaced by separate terms $\beta_1 X$, $\beta_2 X$, $\beta_3 X$, etc. corresponding to categories of the attribute under consideration or, if there was an ordering to the categories involved, by $(\beta + \theta C) X$, where C took values 1, 2, 3, ... and represented the categories, while θ

represented the trend across the ordered categories. If the categorical attribute was not already included in the stratification, appropriate additional categorical covariates were included in models of the form:

$$\frac{\pi}{1-\pi} = e^{\alpha} \left(\sum \gamma_j z_j + \beta x \right) \quad (2)$$

where the z_j are indicator variables representing different levels of the covariates and γ_j are their associated regression coefficients.

Tests of $\beta = 0$ and other hypotheses were carried out using the likelihood ratio and were two-sided where appropriate. However, when considering heterogeneity of β with respect to cell-type, where all the controls were involved in the estimate of β for every cell type, the likelihood ratio

test could not be computed easily. In this case the approximate test-statistic $\sum_{i=1}^n w_i (b_i - \bar{b})^2$ was used, where n was the number of cell types involved, the b_i were the estimates of β for the individual cell types, \bar{b} was the weighted average of the b_i and the w_i were the inverses of the estimated variances of the b_i . The test-statistic was interpreted by comparison with the χ^2 distribution on $n-1$ degrees of freedom.

In order to examine the goodness of fit of various different models, the main analysis was repeated with both linear and quadratic terms in radon, *i.e.* using the equation:

$$\frac{\pi}{1-\pi} = \exp(\alpha)(1 + \beta_1 x + \beta_2 x^2),$$

rather than equation (1).

Analyses that considered categorical, rather than continuous, measures of radon were based on the log-linear model:

$$\frac{\pi}{1-\pi} = \exp(\alpha) \exp(1 + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4 + \dots), \quad (3)$$

where $x_1, x_2, x_3, x_4, \dots$, denote indicator variables corresponding to the categories of radon. A further goodness of fit test was carried out by testing whether the inclusion of terms representing the categories of radon, as in equation (3), gave any improvement in fit over the model given in equation (1).

For analyses based on categorical measures of radon confidence intervals were based on asymptotic standard errors. However, when calculating confidence intervals for the β_i , it seemed undesirable to regard one category as a fixed baseline and present confidence intervals for the other categories relative to it. This would have meant that the confidence intervals for the other pairs of categories could not be easily interpreted, because they would not be independent but would both be substantially influenced by the variability in the baseline category. Therefore, floated variances³ were calculated for each of the β_i . This provided confidence intervals for each category that were all approximately independent of each other and so could more easily be interpreted.

For analyses that considered radon as a continuous variable, the relative risk was set to 1 at zero radon exposure. For estimates of risk based on categorical measures of radon it seemed desirable to choose the arbitrary constant in the relative risk in such a way as to make the categorical analysis compatible with the corresponding continuous analysis. To achieve this, for each categorical analysis, the arbitrary constant was chosen to minimize the sum of the weighted squared distances of the categorical estimates from the regression line for the corresponding analysis based on radon as a continuous variable, with weights set equal to the inverse of the approximate variances of the relative risks. These approximate variances were calculated from the floated variances of the β_i using a Taylor series expansion.

Additional analyses based on measured radon

An upper confidence limit on any possible threshold was computed with the method used previously in analyses of the atomic bomb survivors.⁴ For a postulated threshold exposure, t , the radon exposure, X , was transformed to X_t , where $X_t = 0$ for $X < t$ and $X_t = X - t$ for $X \geq t$. The model in equation (1) was then fitted with X replaced by X_t . This procedure was repeated for $t = 10, 20, 30, \dots$ Bq m⁻³ and the confidence interval derived from the profile of the resulting conditional likelihoods.

If the effects of radon and smoking combined together in an additive fashion, then their combined effect on the odds of lung cancer could be represented by:

$$\frac{\pi}{1 - \pi} = e^{\alpha} (1 + \beta x + \gamma z),$$

where α , β , and X are as in equation (1), Z represents a subject's smoking history, and γ describes the effect of smoking on the odds of lung cancer. If smoking is considered as a categorical variable, this model can be rewritten as:

$$\frac{\pi}{1-\pi} = e^{\alpha} (1 + \beta X + \bar{\delta}_i),$$

where $\bar{\delta}_i$ represents the effect of smoking in the different categories (lifelong non-smokers, current smokers of <15, 15-24, and 25+ cigarettes per day, and ex-smokers of <10 and 10+ years duration, separately for each sex). If, however, the different smoking categories all correspond to different strata, then this model is equivalent to the model:

$$\frac{\pi}{1-\pi} = e^{\alpha_i^*} (1 + \beta_i X),$$

where β_i varies across the different smoking categories according to the relation $\beta_i = \beta / (1 + \bar{\delta}_i)$ and $(1 + \bar{\delta}_i)$ is the relative risk of lung cancer for individuals in smoking category i compared with lifelong non-smokers and α_i^* differs from α in that it takes this relation into account. Therefore, in order to test whether the data were compatible with an additive effect of smoking, the following model was fitted to the data:

$$\frac{\pi}{1-\pi} = e^{\alpha_i^*} \{1 + \beta X / (1 + \bar{\delta}_i)\},$$

where $\bar{\delta}_i$ is the proportionate increase in risk for subjects in smoking category i compared with lifelong non-smokers of the same sex and, as before, i indicates categories of smoking for each sex. The values of $\bar{\delta}_i$ were assumed known and were taken from an analysis of the effects of smoking in these data.⁵ The fit of this model was then compared with the fit of a model in which β_i was allowed to vary freely across the different smoking categories.

The percentage of controls estimated to be lifelong non-smokers in categories of measured radon, after adjusting for study, age, sex, and current region of residence within study, was derived by first estimating the odds ratio of being a lifelong non-smoker in each radon category. The percentage of controls with measured radon <100 Bq/m³ was set equal to that observed.

Adjustment for random uncertainties in the assessment of radon exposures

Measurements of radon gas made in the same dwelling in different years show considerable variability, indicating substantial random uncertainty in the assessment of the long-term average radon concentration in a dwelling over a period of several years from a measurement taken during a single year.⁶⁻⁸ The sources of this variation include uncertainties in the measurement process itself, and also variation in the true radon concentration in the dwelling due, for example, to year-to-year variation in the weather, variation in the lifestyle of those living in the dwelling, and any alterations to the dwelling. Regression coefficients calculated using measurements that are subject to appreciable random variability of this type (usually referred to as classical or measurement error in the statistical literature) are known to suffer from bias unless special methods of analysis are used which take them into account.⁹⁻¹¹ In the present data, in addition to the uncertainty that is present in the radon measurements, there are also uncertainties present in the time-weighted average radon concentrations due to the fact that for many subjects radon measurements are not available for some of the dwellings occupied during the 30-year period of interest but have been estimated indirectly. Uncertainties of this type (usually referred to as Berkson error in the statistical literature) will also cause some bias in the present situation, where the response variable is binary.¹⁰ To correct for the biases caused by both types of uncertainty, the main analyses were repeated taking them explicitly into account.

Measurements of residential radon concentrations from representative samples of dwellings in a given geographical district have been shown on many occasions to be approximately log-normally distributed. In addition, analyses of repeated measurements of radon made in the same dwelling have shown that the size of the variability associated with repeated measurements made in the same dwelling in different years tends to increase as the radon concentration increases, but that after logarithmic transformation the variability is approximately independent of the radon concentration.¹⁰⁻¹² Therefore, in the analyses which adjusted for uncertainties, it was assumed that within each geographical district the true (ie long-term average over many years) radon concentrations varied between dwellings with a log normal distribution and it was also assumed that, on a log scale, the variability associated with repeated measurements in the same dwelling in different years was normally distributed about the true radon concentration for the dwelling.

From the above, if Z_t and Z_m denote the logarithms of the true and the measured radon concentrations in a dwelling respectively and ε_m denotes the difference between the logarithm of the true and the logarithm of the measured radon concentration, then $Z_m = Z_t + \varepsilon_m$, and $Z_t \sim N(\mu, V_t)$, where μ is the mean of the logarithm of the true long term average radon concentrations in the district, and $\varepsilon_m \sim N(0, V_m)$. It therefore follows from Bayes' theorem that for dwellings for which a radon measurement was available the logarithm of the true radon concentration given the measured value would have the following distribution:

$$Z_t | Z_m \sim N \left\{ \frac{(\mu/V_t + Z_m/V_m)}{(1/V_t + 1/V_m)}, \frac{1}{(1/V_t + 1/V_m)} \right\}, \quad (4)$$

while for dwellings for which no radon measurement was available, the true long term radon concentration would have the following distribution:

$$Z_t \sim N \{ \mu, V_t \}. \quad (5)$$

No information on V_m was provided by the data collected within the studies contributing to the Collaborative Analysis. Therefore, all the information that was available from other sources on the variability of repeated measurements made in the same house in different years was assembled and used to indicate appropriate values for V_m for each study.⁵ The values used were: Czech Republic: 0.12; Finland (both studies): 0.33; Italy: 0.03; Sweden (all three studies): 0.14; United Kingdom: 0.20. For the remaining studies, conducted in countries where no repeat measurements were available, the median of these values (0.14) was used. Each study was taken to be a separate geographical district and, within each study, the sample mean and variance of the logarithms of the measurements made on the dwellings for control subjects were used to derive estimates of μ and $(V_t + V_m)$. For the four studies where area-specific estimates had been used to estimate the radon concentrations for dwellings that could not be measured (Austria, Czech Republic, Italy, United Kingdom), separate estimates of μ and $(V_t + V_m)$ were constructed for each area wherever sufficient data were available to allow such estimates to be constructed.

Maximum likelihood estimates of β taking account of the error structure described above were derived by integrating the likelihood over the unknown true radon measurement.¹³ These estimates were calculated using simulation. For each individual in the Collaborative Analysis a

value of the true radon concentration for each dwelling occupied during the 30-year period of interest was generated, using the distribution in equation (4) where it had been possible to measure the radon concentration of the dwelling, or equation (5) where the radon concentration had been estimated indirectly rather than measured. The time-weighted average radon concentration corresponding to these simulated true radon values was then calculated using the same weights as previously and the conditional likelihood corresponding to equation (1) was evaluated for a range of values of β . This procedure was repeated a number of times for the same set of values of β . The average of the simulated likelihoods was then determined and its maximum taken to be the estimated value of β , and likelihood based confidence intervals derived. This method was used, rather than averaging the maximum values of the individual simulated likelihoods, as such a procedure leads to biased estimates of β .¹³ Investigation showed that stable estimates of β were derived when the number of simulations was set at 2000 and so this number was used throughout. A sensitivity analysis was carried out varying the values of the repeated measurement variances (V_m). When they were reduced by 30% the estimate β decreased from 16% (95% CI 5, 31) to 14% (95% CI 5, 27), while when they were increased by 30% the estimate of β increased to 19% (95% CI 6, 41).

The methods that had been developed previously to take uncertainties in the assessment of radon exposure into account in the analysis of the United Kingdom study¹⁰ were not used in the present analysis because it was desirable, in the present analysis, to use the linear odds model given in equation (1), rather than a linear logistic model, and it was also desirable to fit conditional models that adjusted for confounders through stratification. Neither of these aspects can be easily accommodated using the previous methodology.

In addition to the analysis based on the method of integrated likelihood, a time-weighted average "usual" radon concentration was estimated for each individual in the Collaborative Analysis by replacing every measured radon concentration in the time-weighted average by the expected value of the corresponding distribution of true radon concentrations given the measured value, using the distribution for the true log radon concentration given in either equation (4) or equation (5) above. These usual values were also used to derive usual radon concentrations for groups of subjects subdivided into categories according to their original *measured* radon concentrations. The

main analyses were also repeated using a regression calibration method in which the standard methods ignoring uncertainties in the assessment residential radon concentrations were applied but with the estimated usual radon concentrations in place of the measured ones. The integrated likelihood method is theoretically preferable to the regression calibration method, as the regression calibration method does not fully take account of the additional variability introduced by the uncertainties but, in fact, the results using the two methods were very similar.⁵

Combined effect of smoking history and radon exposure on lung cancer risk

Variation in the proportionate increase in risk of lung cancer per unit increase in radon exposure in groups of subjects with different smoking habits was studied using the methods described above. However, it was desirable also to provide some estimates of the combined risks of smoking and radon. It was to be expected that the major determinant of the absolute value of the lung cancer risk for the majority of the subjects in the study would be their smoking history. It was also to be expected that, for individuals with identical radon exposure histories who were also current or ex-smokers, lung cancer risks would vary substantially depending on the details of their smoking histories, including the age at which they started to smoke, the amount of each product smoked at each age and, for ex-smokers, the time since they had given up the habit. Within any population the risk associated with cigarette smoking takes many decades to mature.¹⁴ Cigarette smoking became popular at different times in the different countries in which the component studies of the Collaborative Analysis were carried out, and also became popular among men and among women at different times within most of the countries included in the present study.¹⁵ Therefore, direct modelling of the combined effects of smoking and radon for the data in the Collaborative Analysis would have had to allow for the fact that smoking risks differ substantially from country to country¹⁶ and between men and women within any country. Such direct modelling would have required very complex models and would have led only to imprecisely estimated risks for subjects with any particular smoking history. This did not seem desirable. Instead, estimates of the combined effect of radon and smoking were calculated for current smokers of 15-24 cigarettes per day by assuming that, for any given radon concentration, the relative risk of lung cancer for the current smokers was known precisely and was equal to the overall relative risk that was seen for all males in that smoking category compared with all male lifelong non-smokers. Relative risks of the

effect of smoking in females were not used as, in the present studies, many of the women who were current smokers did not start smoking until well into adult life. More recently most of the women smokers in these European countries have tended to start smoking at a much earlier age. Therefore, the observed relative risks associated with smoking for women in these studies are likely to underestimate substantially the risks of smoking that will result from present smoking patterns in women.¹⁴

The cumulative risk of death from lung cancer at various ages was calculated by assuming that the age-specific death rate from lung cancer among lifelong non-smokers exposed to the mean residential radon concentration observed in the United States (46 Bq m⁻³) was equal to that observed in males in a prospective study of one million individuals carried out by the American Cancer Society (ACS) during the 1980s.¹⁷ Calculations were based on the rates for males only, as rates in males and females were virtually identical. These rates were used in preference to rates based on European data, as they are based on a very much larger sample than any European data, including 316 deaths, and they are consistent with the findings of the two main European studies that provide data on the death rate from lung cancer in lifelong non-smokers [Swedish Longitudinal Smoking study: 26 deaths observed (95% confidence interval: 17.0, 38.1);¹⁸ 20.7 expected based on the ACS rates. British Doctors' study 18 deaths observed (95% confidence interval: 10.7, 28.4); 19.9 expected based on the ACS rates¹⁹]. The hypothetical death rate at each age in lifelong non-smokers with zero radon exposure was calculated from the ACS rates assuming a linear relationship between radon exposure and mortality from lung cancer. The death rates at each age among lifelong non-smokers with no radon exposure were then combined with the relative risk for the current smokers for all the studies combined and the relative risks of radon exposure at various levels to provide estimates of the absolute death rate at each age-group for individuals in various smoking histories and with various radon exposures. Cumulative death rates up to age 75 were calculated by summing the relevant age-specific death rates and these were converted into percentage cumulative risks using the equation $100 \times \{1 - \exp(-c)\}$, where c is the relevant cumulative death rate.

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