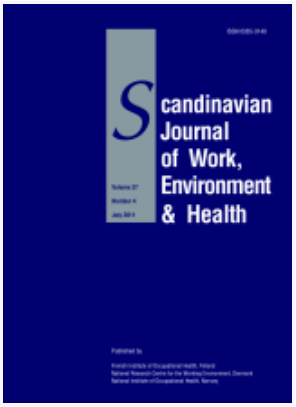

Supplement

Scand J Work Environ Health 2006;32 suppl 1:1-84

Residential radon and lung cancer—detailed results of a collaborative analysis of individual data on 7148 persons with lung cancer and 14 208 persons without lung cancer from 13 epidemiologic studies in Europe

by Darby S, Hill D, Deo H, Auvinen A, Barros-Dios JM, Baysson H, Bochicchio F, Falk R, Farchi S, Figueiras A, Hakama M, Heid I, Hunter N, Kreienbrock L, Kreuzer M, Lagarde F, Mäkeläinen I, Muirhead C, Oberaigner W, Pershagen G, Ruosteenoja E, Schaffrath Rosario A, Tirmarche M, Tomášek L, Whitley E, Wichmann H-E, Doll R

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Residential radon and lung cancer—detailed results of a collaborative analysis of individual data on 7148 persons with lung cancer and 14 208 persons without lung cancer from 13 epidemiologic studies in Europe

by Sarah Darby,[1] David Hill,[1] Harz Deo,[2] Anssi Auvinen,[3] Juan Miguel Barros-Dios,[4] Hélène Baysson,[5] Francesco Bochicchio,[6] Rolf Falk,[7] Sara Farchi,[8] Adolfo Figueiras,[4] Matti Hakama,[9] Iris Heid,[10] Nezahat Hunter,[11] Lothar Kreienbrock,[12] Michaela Kreuzer,[13] Frédéric Lagarde,[14] Ilona Mäkeläinen,[15] Colin Muirhead,[11] Wilhelm Oberaigner,[16] Göran Pershagen,[14] Eeva Ruosteenoja,[15] Angelika Schaffrath Rosario,[10] Margot Tirmarche,[5] Ladislav Tomášek,[17] Elise Whitley,[18] Heinz-Erich Wichmann,[10] Richard Doll[1]

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This report is dedicated to the memory of Olav Axelson (1937–2004), who, following the observation that decreased ventilation as a result of energy-saving measures had been leading to increased residential radon concentrations in Sweden, published the first study specifically designed to examine the effect of residential radon concentrations on the risk of lung cancer

(Axelson O, Edling C, Kling H. Lung cancer and residency—a case-referent study on the possible impact of exposure to radon and its daughters in dwellings. Scand J Work Environ Health 1979;5:10–5.)

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Abstract

Darby S, Hill D, Deo H, Auvinen A, Miguel Barros-Dios J, Baysson H, Bochicchio F, Falk R, Farchi S, Figueiras A, Hakama M, Heid I, Hunter N, Kreienbrock L, Kreuzer M, Lagarde F, Mäkeläinen I, Muirhead C, Oberaigner W, Pershagen G, Ruosteenoja E, Schaffrath Rosario A, Tirmarche M, Tomášek L, Whitley E, Wichmann H-E, Doll R. Residential radon and lung cancer—detailed results of a collaborative analysis of individual data on 7148 persons with lung cancer and 14 208 persons without lung cancer from 13 epidemiologic studies in Europe. *Scand J Work Environ Health* 2006;32 suppl 1:1–84.

Objectives Studies seeking direct estimates of the lung cancer risk associated with residential radon exposure lasting several decades have been conducted in many European countries. Individually these studies have not been large enough to assess moderate risks reliably. Therefore data from all 13 European studies of residential radon and lung cancer satisfying certain prespecified criteria have been brought together and analyzed.

Methods Data were available for 7148 persons with lung cancer and 14 208 controls, all with individual smoking histories and residential radon histories determined by long-term radon gas measurements.

Results The excess relative risk of lung cancer per 100 Bq/m^3 increase in the observed radon concentration was 0.08 [95% confidence interval (95% CI) 0.03–0.16; P=0.0007] after control for confounding. The dose-response relationship was linear with no evidence of a threshold, and it remained significant when only persons with observed radon concentrations of <200 Bq/m^3 were included. There was no evidence that the excess relative risk varied with age, sex, or smoking history. Removing the bias induced by random uncertainties related to radon exposure assessment increased the excess relative risk of lung cancer to 0.16 (95% CI 0.05–0.31) per 100 Bq/m^3. With this correction, estimated risks at 0, 100, and 400 Bq/m^3, relative to lifelong nonsmokers with no radon exposure, were 1.0, 1.2, and 1.6 for lifelong nonsmokers and 25.8, 29.9, and 42.3 for continuing smokers of 15-24 cigarettes/day.

Conclusions These data provide firm evidence that residential radon acts as a cause of lung cancer in the general population. They provide a solid basis for the formulation of policies with which to manage risk from radon and reduce deaths from the most common fatal cancer in Europe.

Executive summary

Background

The radioactive gas radon is the most important natural source of human exposure to ionizing radiation. In most countries, the majority of the exposure is received indoors, especially in houses and other dwellings. Radon is known to be a human carcinogen and studies of underground miners exposed occupationally, and usually at very high concentrations, have consistently demonstrated an increased risk of lung cancer for both smokers and nonsmokers. However, there is little direct information on the risk of lung cancer that is associated with exposure to residential radon, for which concentrations are usually much lower than those of miners and the conditions of exposure are different.

Material and methods

Thirteen studies of residential radon and lung cancer that satisfy certain prespecified criteria have been carried out in Europe. The studies were performed in Austria, the Czech Republic, Finland (2 studies), France, Germany (2 studies), Italy, Spain, Sweden (3 studies), and the United Kingdom. Individual data from all of these studies have been assembled in a uniform manner. Data on smoking history and also on radon exposure history, based on long-term measurements of radon gas concentrations, were available for a total of 7148 persons with lung cancer and 14 208 controls. Among the people with lung cancer, the mean time-weighted observed average residential radon concentration during the 30-year period ending 5 years prior to diagnosis was 104 Bq/m^3. The ratio of the number of controls to the number of cases differed between the different studies, and the weighted mean observed residential radon concentration for the controls, with weights proportional to the study-specific numbers of cases, was 97 Bq/m^3. The difference between the mean for the cases and the weighted mean for the controls differed highly significantly from zero (P=0.0002). The association between the risk of developing lung cancer and residential radon concentrations in these data was studied using linear models for the relative risk, with stratification for study, age, sex, region of residence within each study, and detailed smoking history. Analyses were carried out first in relation to the observed radon concentration without making any adjustment for the effect of random uncertainties in the assessment. The major analyses were then repeated with an approximate adjustment to take these uncertainties into account.

Results

There was clear evidence (P=0.0007) of an association between the residential radon concentration during the previous 35 years and the risk of lung cancer. The dose–response relationship was linear, and the estimated excess relative risk of lung cancer was 0.08 [95% confidence interval (95% CI) 0.03–0.16] for a 100 Bq/m^3 increase in the time-weighted average observed radon concentration. When the analysis was repeated for only people with observed radon concentrations of <200 Bq/m^3, the dose–response relationship remained significant (P=0.04), and the estimated excess relative risk per 100 Bq/m^3 was similar to that based on the entire dataset. Models that allowed for a possible threshold concentration did not provide a significant improvement in fit when compared with a model in which risk was proportional to the radon concentration, even for very low concentrations (P=0.44), and the upper 95% confidence limit for a possible threshold was 150 Bq/m^3.

There was no evidence that the dose–response relationship varied between the different studies (P=0.94), nor were the results dominated by any individual study. In addition, there was no significant evidence that the dose–response relationship depended on the detailed aspects of the study design or on the characteristics of the radon measurements or by age, sex, or smoking status. When lifelong nonsmokers were considered separately, the estimated excess relative risk of lung cancer was 0.11 (95% CI 0.00–0.28, P=0.04) per 100 Bq/m^3 observed radon concentration.

When small-cell lung cancers and lung cancers of other histological types were examined separately, there was evidence (P=0.03) that the dose–response relationship was steeper for small-cell lung cancer than for other histological types. The estimated excess relative risk for small-cell lung cancer was 0.31 (95% CI 0.13–0.61) per 100 Bq/m^3 observed radon concentration. For adenocarcinoma the estimated excess relative risk per 100 Bq/m^3 observed radon concentration was 0.06 (95% CI <-0.03–0.20), and, for squamous-cell and other histologically confirmed types, the estimates were -0.01 (95% CI <-0.03–0.09) and 0.04 (95% CI <-0.03–0.24), respectively. For all of the confirmed histologies other than small-cell lung cancer, the estimated excess relative risk

was 0.03 (95% CI <-0.03–0.10) per 100 Bq/m^3 observed radon concentration.

After an approximate adjustment was made for the effects of random uncertainties in the assessment of radon concentrations, the dose–response relationship remained linear, and the estimated excess relative risk per 100 Bq/m^3 increased to 0.16 (95% CI 0.05–0.31). This risk is slightly lower, but compatible with, the risk that has been postulated on the basis of studies of radon-exposed underground miners.

There was no evidence that the excess relative risk per unit increase in the observed radon concentration varied with the smoking status of the person (P=0.92). Therefore, in analyses of the joint effects of smoking and radon exposure, the effect of radon on relative risk was assumed to be the same, regardless of smoking status. For lifelong nonsmokers, the risks of lung cancer at corrected radon concentrations of 100 and 400 Bq/m^3 were estimated to be 1.2 and 1.6, respectively, relative to the risk for lifelong nonsmokers at 0 Bq/m^3. Combining the excess relative risk for radon with the relative risks for different categories of smoking status determined for the men in these data suggests that the risks to smokers of 15–24 cigarettes per day, relative to lifelong nonsmokers exposed at 0 Bq/m^3, are 25.8 at 0 Bq/m^3 and 29.9 and 42.3 at corrected radon concentrations of 100 and 400 Bq/m^3, respectively, while the risks for ex-smokers of <10 years' duration are 20.8, 24.2, and 34.2 at 0, 100, and 400 Bq/m^3, respectively.

When the data from these European case–control studies were combined with external data on the absolute risk of death from lung cancer, the cumulative risks of death from lung cancer by the age of 75 years in the absence of radon exposure were estimated to be 0.41% and 10.11% for lifelong nonsmokers and continuing smokers of 15–24 cigarettes per day, respectively. These cumulative risks increased with increasing radon concentration, reaching 0.47% for lifelong nonsmokers and 11.63% for continuing cigarette smokers at a corrected radon concentration of 100 Bq/m^3, 0.67% for lifelong nonsmokers, and 16.03% for continuing cigarette smokers at 400 Bq/m^3. For those who gave up smoking, the cumulative risks in the first 10 years would be about 80% of those for continuing smokers. Thereafter they would be lower, but they cannot be estimated precisely from the data in the present study.

Conclusions

These data provide firm evidence that residential radon acts as a cause of lung cancer in the general population. The results are crucial to the development and refinement of policies to manage exposure to this form of natural radiation so as to reduce the annual number of deaths from the most common type of fatal cancer in Europe.

A short report summarizing the main findings of this study has been published elsewhere (Darby S, Hill D, Auvinen A, Barros-Dios JM, Baysson H, Bochicchio F et al. Radon in homes and lung cancer risk: a collaborative analysis of individual data from 13 European case-control studies. BMJ 2005;330:223–7).

Introduction

Radon-222 is a chemically inert radioactive gas that has a half-life of 3.8 days and gives rise to a series of short-lived radioactive decay products. Radon arises naturally from the decay chain of uranium-238, which is present throughout the earth's crust, and it seeps out of rocks and soil before decaying, by emission of an alpha particle, into a series of short-lived radioactive progeny. Two of these, polonium-218 and polonium-214, also decay by emitting alpha particles. If inhaled, radon itself is mostly exhaled immediately. However, its short-lived progeny, which are solid, tend to be deposited on the bronchial epithelium and, as a result, sensitive cells may be exposed to alpha radiation.

Radon concentrations are usually very low in outdoor air, but concentrations can build up in situations in which it is unable to disperse readily. Some of the highest radon concentrations occur in underground mines of uranium and other igneous rocks, but concentrations in dwellings and other buildings are also often appreciably higher than those in outdoor air. Worldwide it is estimated that the average annual effective dose from radon and its decay products is 1.15 mSv and that it is responsible for almost 50% of the total effective dose from all sources of natural radiation (1). In most countries, the majority of the exposure is received indoors, especially in houses and other dwellings, where the principal source is usually the subsoil under the building, although, under some circumstances, appreciable exposure may occur from building materials or from radon dissolved in water. Residential radon concentrations vary greatly, depending on local conditions, and, in many countries, the concentrations normally observed vary over two orders of magnitude or more.

Studies of underground miners exposed to high concentrations of radon have consistently shown an increased risk of lung cancer for both smokers and non-smokers (2). Similar observations have been made in experimental studies on rats and dogs, and radon has been classified as a human carcinogen by the International Agency for Research on Cancer (3, 4). On the basis of estimates of the risk of lung cancer derived from studies of underground miners, it has been suggested that, in many countries, residential radon may be the cause of a considerable proportion of lung cancers. This possibility has potential public health relevance, as it is possible both to reduce indoor radon levels in most existing buildings at moderate cost and to ensure that radon concentrations are negligible in new buildings for a reasonable or low cost. Calculations of the probable numbers of lung cancers caused by residential radon depend, however, on several assumptions. One of these assumptions concerns the extent to which estimates of the lung cancer risk derived from studies of underground miners are applicable to residential situations. The information on the concentrations of radon gas and its decay products to which the miners were exposed is crude and subject to sizeable errors. Conditions of exposure are very different in mines and homes, and the differences affect the typical radiation dose to the lung cells for a given concentration of radon gas. The studies of miners, moreover, provide information only about the effects of radon exposure to adult males, most of whom were exposed for only a few years and at much higher concentrations than usually occur in dwellings. Some of the miners were also exposed to other carcinogens, such as arsenic or silica, and, although many of them are thought to have been cigarette smokers, little or no information is available about their smoking habits. All of these factors mean that there is considerable uncertainty over the extent to which the estimates of the lung cancer risk derived from studies of underground miners are applicable to exposure to residential radon.

A direct estimate of the risk of lung cancer associated with residential radon would avoid many of these uncertainties, and, in several countries, studies have been carried out that have sought to provide such an estimate. However, the studies have had limited power to detect the effects of residential radon, and none has provided a sufficiently precise estimate of the risk. Greater precision can be obtained by combining information from several studies, but it is impossible to combine the data in a satisfactory manner on the basis of only the published information from the various studies. This difficulty is partly because exposure to radon decay products has been categorized somewhat differently in the various publications and partly because confounding with smoking is dealt with in different ways by the different studies. Urban areas tend to have lower radon concentrations than rural ones, as the underlying rock is usually sedimentary and urban residents live upstairs in apartments more often than rural residents. Urban areas also usually have a high smoking prevalence. Hence radon levels in homes tend to be negatively correlated with smoking, and a large dataset, with detailed information on smoking in a uniform format for all persons, is needed if this correlation is to be corrected for reliably. In the Collaborative Analysis of Individual Data on 7148 Persons with Lung Cancer and 14208 Persons

without Lung Cancer from 13 Epidemiologic Studies in Europe, we have therefore brought together individual data from all of the studies of residential radon and lung cancer that have been carried out in Europe and satisfy certain criteria laid down in advance, with the objectives of investigating the consistency of the different studies and of estimating more precisely the change in lung cancer risk associated with increasing residential radon concentration and the extent to which it is modified by factors such as age, sex, and smoking history. A short report summarizing the main findings of this study has been published elsewhere (5).

Materials and methods

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 persons with lung cancer (to be referred to as lung cancer cases); controls had been selected in such a way as to be representative of the population from which the lung cancer cases had been drawn; detailed residential histories going back at least 15 years had been compiled in a similar way both for the lung cancer cases and the controls; long-term (minimum 2 months) measurements of radon gas concentrations 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 most of the 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 lung cancer cases and 150 controls. A total of 13 studies satisfied these criteria, carried out in Austria, the Czech Republic, Finland (2 studies), France, Germany (2 studies), Italy, Spain, Sweden (3 studies), and the United Kingdom (table 1). All of these studies were included in the Collaborative Analysis.

Table 1. European case-control studies of residential radon and lung cancer.

Study	Years of diagnosis for the lung cancer cases
Austria: Oberaigner et al, 2002 (6)	1970–1992
Czech Republic: Tomášek et al, 2001 (7)	1960–1999
Finland nationwide: Auvinen et al, 1996 (8)	1986–1992
Finland southern: Ruosteenoja et al, 1996 (9)	1979–1985
France: Baysson et al, 2004 (10)	1990–1999
Germany eastern: Wichmann et al, 1999 (11); Kreuzer et al, 2003 (12); Wichmann et al (13)	1991–1997
Germany western: Wichmann et al, 2005 (13); Wichmann et al, 1998 (14); Kreienbrock et al 2001, (15)	1990–1995
Italy: Bochicchio et al, 2005 (16)	1993–1996
Spain: Barros-Dios et al, 2002 (17)	1992–1994
Sweden nationwide: Pershagen et al, 1994 (18); Lagarde et al, 1997 (19)	1980–1984
Sweden never-smokers: Lagarde et al, 2001 (20)	1978–1995
Sweden Stockholm: Pershagen et al, 1992 (21)	1983–1987
United Kingdom: Darby et al, 1998 (22)	1988–1995

Design of the studies included in the Collaborative Analysis

Twelve of the thirteen studies had been designed as case–control studies, while in the Czech study, which was originally a cohort study, all of the lung cancer cases were included in the Collaborative Analysis, together with four controls per case, chosen from the original cohort according to a nested case–control design. Seven of the studies had enrolled recently diagnosed cases of lung cancer prospectively (France, Germany eastern, Germany western, Italy, Spain, Sweden Stockholm, United Kingdom), while the remainder (Austria, Czech Republic, Finland nationwide, Finland southern, Sweden nationwide, Sweden never-smokers) had identified some or all of the lung cancer cases retrospectively using high-quality cancer registries or death indices. For most of the studies, the years of diagnosis for which the lung cancer cases were included lay in the 1980s and 1990s, but the use of retrospective data sources enabled the inclusion of cases from the 1970s or, in some, even the 1960s (Austria, Czech Republic, Finland southern, Sweden never-smokers) to be included (see table 1).

In most of the studies, information on the diagnosis of lung cancer was taken from hospital records or cancer

registries, and all of the persons whose final diagnosis was lung cancer were included in the study irrespective of whether or not microscopic information had been obtained. However, in the German studies, only microscopically confirmed cases of lung cancer were included, while in the Austria and Czech Republic studies diagnoses were based on death certificates only. Three studies (France, Italy, and United Kingdom) included only persons who were long-term residents of the defined study area, and one study (Finland nationwide) included only persons who had lived in the same single family house for at least 19 years. Most of the studies included both men and women, but the Finland southern study included only men and the Sweden Stockholm study included only women. In five studies (France, Germany eastern, Germany western, Sweden nationwide, United Kingdom) people were included in the study only if they were under 75 years of age, while, in the remaining studies, there was no upper age limit.

Most of the studies included only population-based controls, but three (Sweden never-smokers, Sweden Stockholm, and United Kingdom) included both hospital and population controls, and two (France and Italy) included only hospital controls. In most of the studies, the controls were matched to lung cancer cases by sex and age or year of birth, while, the Sweden nationwide study, was matched for age but not sex, and in the Spain and Sweden Stockholm studies no age matching was carried out. In six studies (France, Germany eastern, Germany western, Spain, Sweden never-smokers, United Kingdom) the control group was matched to the lung cancer cases for geographic region of current residence, while, for the remaining studies, no geographic matching was carried out within the area selected for study.

Additional selection criteria were used for the controls in some studies. In three studies (France, Italy, and United Kingdom) hospital controls were selected from people whose current hospital admission was for a disease not strongly related to smoking. In the Sweden never-smokers study, all of the members of the control group were also lifelong nonsmokers. In the Austria study, where all the lung cancer cases had died, the controls were chosen from those who had also died and whose cause of death was not strongly related to smoking. The controls in the Austria study were also matched to lung cancer cases by year of death. In the Swedish nationwide study, one of the two control groups was matched to the lung cancer cases by vital status.

In the Finland southern study, an initial screening questionnaire was used to determine the smoking status of potential members of the control group; among those who replied, all of the current smokers were selected for the study, as were random samples of approximately 10% each of ex-smokers and lifelong nonsmokers. Before the main collaborative analysis, preliminary analyses were carried out on the data from the Finland southern study and the Swedish nationwide study to ascertain whether it was necessary to account specifically for these aspects of study design in the analysis. It was concluded that no special adjustment was necessary.

In six of the studies (France, Germany eastern, Germany western, Italy, Sweden Stockholm, United Kingdom), people were not included unless they were in a position to provide information personally, while, in the Austria study, all of the information was supplied by surrogates, as all of the people in that study had already died, and, for the remaining studies, information was accepted from both the study subjects themselves and their surrogates. Most of the studies collected data from the study subjects or their surrogates in person, but the primary method of data collection was by mail in the nationwide studies in Finland and Sweden, and also in a part of the Swedish study of never-smokers. Additional details of the method used for selecting the cases and controls are given in appendix A (table A1).

Period of interest for exposure to radon

In the Collaborative Analysis, it was assumed that the period of residential radon exposure that is relevant to the risk of lung cancer at a particular point in time is the 30-year period ending 5 years prior to the index date. This period was chosen on the basis of the studies of underground miners in which exposure within the previous 5 years and exposure more than 35 years previously were found to have little or no effect on the risk of the disease (2). In order to determine the 30-year period of interest, an index year was determined for each subject. For the lung cancer cases, the index year was usually the year of diagnosis of, or the year of death from, lung cancer, while, for the controls, a suitable date was chosen depending on the study design. [See appendix A (table A1) for further details.]

Radon measurement procedures in the participating studies

In the Czech Republic study the aim was to measure the radon concentration in all of the dwellings occupied by the subjects within the 30-year period of interest, while nine studies (Austria, Finland southern, France, Germany western, Italy, Sweden nationwide, Sweden never-smokers, Sweden Stockholm, and United Kingdom) restricted attention to dwellings that had been occupied for at least 1 or 2 years during the period of interest. In four studies, only one dwelling was considered (the most recent home occupied for at least 2 years in the Austria

study, the current dwelling in the Germany eastern and Spain studies, and the dwelling occupied in 1985 in the Finland nationwide study). Eleven of the studies used closed alpha-track detectors, whereas two studies (Czech Republic, France) used open alpha-track detectors, and, in one study (Sweden Stockholm), the measurements from the alpha-track detectors were supplemented by measurements made with thermoluminescence detectors for dwellings in which no alpha-track measurement was possible. In nine of the studies, two detectors were placed either in the bedroom and living room or in the two most occupied rooms of the dwelling, while, in one study (Italy), two pairs of detectors were placed, one pair in the bedroom and one pair in the living room, and in three studies (Finland nationwide, Finland southern, Spain) one detector only was placed, either in the bedroom or in the living room. When more than one measurement had been made, an appropriately weighted average was calculated to give a single representative value for each dwelling. In five studies (Czech Republic, Finland nationwide, Germany eastern, Germany western, Sweden Stockholm) the detectors were left in place for a full year, in the Austria study they were mostly left in place for a full year, but for shorter periods and with seasonal corrections, in dwellings with high concentrations, and in the Italy study the detectors were in place for two consecutive 6-month periods. In the remaining studies the measurement period was less than a year (range 2–6 months), and seasonal adjustments were applied when necessary. Additional details of the radon measurement procedures in the various studies are given in appendix A (table A2).

Data on individual persons in the study

For each person included in the study, information was compiled on all the variables necessary for the Collaborative Analysis according to a common data format. [See appendix A (table A3).] The variables included case-control status, interview type and method, sex, index year, age and region of residence during the index year, histological type of cancer (for lung cancer cases), diagnosis (for hospital controls), detailed smoking history, social status, occupational exposure to radon, asbestos or another established occupational lung carcinogen (23), average duration of occupancy of the home during the 30-year period of interest, proportion of 30-year period of interest spent living in an urban area, usual position of the bedroom window at night, number of years spent working outdoors, and exposure to environmental tobacco smoke (for lifelong nonsmokers). As far as was possible, uniform definitions were used across all of the studies even though it was necessary to use study-specific definitions for social status, based either on occupation or on education, depending on the information available within each study. The subjects were included in the analysis only if there was a radon measurement corresponding to at least one dwelling that they had occupied during the 30-year period of interest ending 5 years prior to the index date; their smoking history was available; and, for the lung cancer cases, the final diagnosis was primary cancer of the trachea, bronchus, or lung [International Classification of Diseases (ICD), 9th revision, code 162 (24), but excluding carcinoid tumors]. Details of the numbers of persons included in the Collaborative Analysis, both in relation to the original study publication and to the total number of persons initially selected for the study are given in appendix A (table A4).

For each person, information was also sought on the measured radon gas concentration for each dwelling during the 30-year period of interest and on the geographic area of residence (or, for the Sweden Stockholm study, the type of dwelling) where the person had been living. Proxy measurements made in dwellings close to the subject's own dwelling were used only in the Italy and Sweden Stockholm studies. For the Italy study, proxy measurements were used only for apartments above ground level, in the same building and, generally, on the same floor as the target dwelling, whereas, in the Sweden Stockholm study, proxy measurements were only used for apartments in the same building and on the same floor as the target dwelling. For years in which no measurement of the person's dwelling was available, estimates were made. Ideally, such estimates would be based on the distribution of radon concentrations in the whole population. In these case–control studies, the controls should, 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 of 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 >10%, and area-specific estimates were used throughout the analysis. For the remaining studies, the reduction in the mean squared error of prediction was <10% and the estimates for missing values were based on the overall mean of the measurements made for the controls. Further details are given in appendix C (table C1).

Statistical methods

Main analyses

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 following linear odds model:

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

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 scale than on an exponential one. In addition, results expressed on a linear scale are more easily applied in the context of radiological protection.

For many analyses x was the time-weighted average (TWA) observed radon concentration for a subject, and it was calculated as $x = \sum_j w_j x_j$, where x_j are the observed radon concentrations, either measured or estimated, corresponding to the dwellings occupied by the person during the 30-year period of interest, and w_j are weights representing the proportion of the 30-year period interest corresponding to each dwelling.

As the probability of developing lung cancer is small, $\pi / (1 - \pi) \approx \pi$ 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 excess relative risk of lung cancer per unit increase in the radon exposure.

Allowance was made for potential confounders either through stratification (ie, by allowing each stratum to have its own α in equation 1) or by including covariates in the model through the addition of categorical terms in the linear part of equation 1:

$$\frac{\pi}{1-\pi} = \exp(\alpha)\left(\sum \gamma_j z_j + \beta x\right), \qquad \text{equation 2}$$

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

Within each stratum, the number of lung cancer cases was assumed to have a binomial distribution with parameters n and π, where n is the total number of persons in the stratum. Models were fitted using conditional maximum likelihood, along the lines usually used in conditional logistic regression using the software packages Epicure (25) and Stata (26). 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, they usually differed appreciably from those based on standard errors. For linear odds models in which more than one parameter was fitted, such as those of the form given in equation 2, confidence intervals were based on the profile of the conditional likelihood. For some analyses the lower limit of the confidence interval, and occasionally also the estimated value of β, could not be evaluated precisely as they were less than $-1/x_{max}$, where x_{max} was the largest value of x, and thus corresponded to negative fitted values for the odds. In such cases, all that could be presented was the fact that the values were 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 $\beta_1 x$, $\beta_2 x$, $\beta_3 x$, and so forth, 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 the model, as in equation 2.

Tests of $\beta = 0$ and other hypotheses were carried out using the likelihood ratio and were two-sided where appropriate. However, when the heterogeneity of β with respect to cell type was considered, where all the controls were included in each estimate, 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, b_i were the estimates of β for the individual cell types, $\bar{b}$ was the average of b_i, and w_i were the inverses of the estimated variances of b_i. The test statistic was evaluated by comparison with the χ^2 distribution on $n - 1$ degrees of freedom.

In order to examine the goodness of fit of different models, some analyses were repeated with both linear and quadratic terms in radon, that is, using the equation: $\pi / (1 - \pi) = \exp(\alpha)(1 + \beta_1 x + \beta_2 x^2)$, rather than equation 1, and some analyses were repeated with a logistic model, that is, one with a log-linear rather than a linear term for radon: $\pi / (1 - \pi) = \exp(\alpha + \beta x)$.

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

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

where x_1, x_2, x_3, x_4, ..., 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 the analyses in which log-linear models were fitted (including those based on categorical measures of radon), confidence intervals were based on asymptotic standard errors. For the analyses based on categorical measures of radon, when confidence intervals were calculated for β_i, it seemed undesirable to regard one category as a fixed baseline and present confidence intervals for the other categories relative to it, as it 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 variances were calculated for each of the β_i (27). This procedure provided confidence intervals for each category that were all approximately independent of each other and so could be more easily interpreted.

For the 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 goal, 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 using 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.

An upper confidence limit on any possible threshold was computed using the method used previously in analyses of atomic bomb survivors (28). 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, … Bq/m^3, and the confidence interval was derived from the profile of the resulting conditional likelihoods.

If the effects of radon and smoking combined in an additive fashion, their joint effect on the odds of lung cancer could be represented by: $\pi / (1 - \pi) = e^{\alpha} (1 + \beta x + \gamma z)$, where α, β, and x are as in equation 1, z represents a person's smoking history, and γ decribes the effect of smoking on the odds of lung cancer. If smoking is considered as a categorical variable, this model can be rewritten as: $\pi / (1 - \pi) = e^{\alpha} (1 + \beta x + \delta_i)$, where δ_i represents the effect of smoking in the different categories (lifelong nonsmokers, 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 corresponded to different strata, then this model is equivalent to the following model: $\pi / (1 - \pi) = e^{\alpha_i^*} (1 + \beta_i x)$, where β_i varies across the different smoking categories according to the relation $\beta_i = \beta / (1 + \delta_i)$, and $(1 + \delta_i)$ is the relative risk of lung cancer for persons in smoking category i compared with lifelong nonsmokers 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: $\pi / (1 - \pi) = e^{\alpha_i^*} [1 + \beta x / (1 + \delta_i)]$, where δ_i is the proportionate increase in risk for persons in smoking category i compared with lifelong nonsmokers of the same sex and, as before, i indicates categories of smoking for each sex. The values of δ_i were assumed to be known and were taken from the analysis of the effects of smoking in these data. 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.

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

The variation in the excess relative risk of lung cancer per unit increase in radon exposure in the groups of persons with different smoking habits was studied using the methods described in the preceding section. 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 most of the persons in the study would be their smoking history. It was also to be expected that, for persons 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 risks associated with smoking take many decades to mature (29). Cigarette smoking became popular at different times in the different countries in which the component studies of the Collaborative Analysis were carried out, and it also became popular among men and women at different times within most of the countries involved (30). Therefore, joint modeling of the effects of smoking and radon for the data in the Collaborative Analysis would have had to allow for the fact that smoking risks differ from country to country (31), and between men and women within any country. Such joint modeling would have required very complex models

and would have led only to imprecisely estimated risks for persons with any particular smoking history. This situation did not seem desirable. Instead, estimates of the joint effect of radon and smoking were calculated for broad categories of smokers by assuming that, for any radon concentration, the relative risk of lung cancer for the persons in each broad smoking category was known precisely and was equal to the relative risk that was seen for all men in that smoking category compared with all male lifelong nonsmokers. Relative risks of the effect of smoking on women 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 female smokers in these European countries have tended to start smoking at a much earlier age and to smoke a similar number of cigarettes per day as men. Studies have shown that women are as susceptible to lung cancer as men, given similar cigarette smoking histories (32). 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 the present smoking patterns of women (29).

The cumulative risk of death from lung cancer at various ages was calculated by assuming that the age-specific death rate from lung cancer for lifelong nonsmokers exposed to the mean residential radon concentration observed in the United States (46 Bq/m^3) was equal to that observed for men in a prospective study of one million people carried out by the American Cancer Society during the 1980s (33). [See appendix A, table A5.] Calculations were based on the rates for men only, as the rates for men and women were virtually identical. The American rates were used in preference to those based on European data, as they are based on a 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 among lifelong nonsmokers {Swedish longitudinal smoking study: 26 deaths observed [95% confidence interval (95% CI) 17.0–38.1] (34) and 20.7 expected based on the rates in table A5 in appendix A; British doctors' study: 18 deaths observed (95% CI 10.7–28.4) and 19.9 expected based on the rates in table A5 in appendix A (35)}. From the rates in table A5 in appendix A, the hypothetical death rate at each age for lifelong nonsmokers with zero radon exposure was calculated on the assumption of a linear relationship between radon exposure and mortality from lung cancer. The death rates at each age for lifelong nonsmokers with no radon exposure were then combined with the relative risk for current smokers for all of the studies combined and with the relative risks at various levels of radon exposure, to provide estimates of the absolute death rate for each age group of people with various smoking histories and with various radon exposures. The cumulative death rates up to the ages of 75, 80, and 85 years were calculated by summing the relevant age-specific death rates, and these were converted into the percentage cumulative risks using the formula $100 \times [1 - \exp(-c)]$, where c is the relevant cumulative death rate.

Method of adjustment for random uncertainties in the assessment of residential radon exposures

Measurements of radon gas made in the same dwelling in different years have shown considerable variability, indicating that, when the radon concentration in a dwelling is assessed from measurements taken during a single year, there is appreciable random uncertainty in the assessment of the long-term average concentration of residential radon in a dwelling over a period of several years. [See, for example, Bochicchio et al, personal communication, Hunter et al (36), Lomas & Green (37).] 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 alterations to the dwelling itself. 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 that take them into account (19, 22, 38, 39). In the present data, in addition to the uncertainty of the measured radon concentrations, there are also uncertainties for the TWA observed radon concentrations due to the fact that, for many persons, radon measurements were not available for some of the dwellings occupied during the 30-year period of interest, and uncertainties of this type (usually referred to as Berkson error in the statistical literature) also cause some bias in the present situation, for which the response variable is binary (38). To correct for the biases caused by both types of uncertainty, the main analyses were repeated with them taken explicitly into account.

Measurements of residential radon concentrations from representative samples of dwellings in a given geographic district have been shown on many occasions to be approximately log-normally distributed. In addition, analyses of repeated radon measurements in the same dwelling have shown that the size of the variability associated with repeated measurements made 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 (38, 40, 41). Therefore, in the analyses that adjusted for uncertainties, it was assumed that,

within each geographic district, the true (ie, long-term average) radon concentrations had a log-normal distribution, and it was also assumed that, on a log scale, the variability associated with repeated measurements in the same dwelling was normally distributed about the true radon concentration for that dwelling.

According to the preceding information, 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 $Z_t \sim \mathrm{N}(\mu, V_t)$, where μ is the mean of the logarithms of the true long-term average radon concentrations in the district, and $\varepsilon_m \sim \mathrm{N}(0, V_m)$. 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:

$$Z_t \mid Z_m \sim \mathrm{N}\left[\frac{(\mu / V_t + Z_m / V_m)}{(1/V_t + 1/V_m)}, \frac{1}{(1/V_t + 1/V_m)}\right], \quad \text{equation 4}$$

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

$$Z_t \sim \mathrm{N}[\mu, V_t]. \quad \text{equation 5}$$

No information on V_m was provided by the data collected in the studies contributing to the Collaborative Analysis. Therefore, all of the information 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. Each study was considered to be a separate geographic district and, within each study, the sample mean and variance of the logarithms of the measurements made on the dwellings for controls were used to derive estimates of μ and $(V_t + V_m)$. For the four studies in which 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 when sufficient data were available to allow such estimates to be constructed.

Maximum likelihood estimates of β, taking into account the error structure described in the previous paragraph, were derived by integrating the likelihood over the unknown true radon measurement. These estimates were calculated using simulation. For each person 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 TWA 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 several times for the same set of values of β. The average of the simulated likelihoods was then determined, and its maximum was considered to be the estimated value of β, and likelihood-based confidence intervals were derived. This method was used, rather than the averaging of the maximum values of the individual simulated likelihoods, as such a procedure leads to biased estimates of β (T Fearn, personal communication). An investigation showed that stable estimates of β were derived when the number of simulations was set at 2000, and therefore this number was used throughout. 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 study (38) 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 models conditional on the total number of persons in each stratum. Neither of these aspects can be easily accommodated using the previous methodology.

In addition to the analyses in which the uncertainties in the assessment of radon concentrations were taken into account by the method of integrated likelihood, additional analyses were carried out in which a TWA corrected radon concentration was calculated for each person in the Collaborative Analysis. These TWA corrected radon concentrations were derived by assuming that every measured or estimated radon concentration was equal to the expected value of the corresponding distribution of the true radon concentrations given the observed value, using the distribution for the true log radon concentration given in either equation 4 or equation 5. These corrected values were used to derive the mean corrected radon concentrations for groups of persons. The main analyses were then repeated using a regression calibration method in which the standard methods used in the previous section were applied, but with the corrected radon concentrations in place of the observed ones. The regression calibration technique has been shown to provide reasonable adjusted-point estimates in nonlinear dose-effect relationships (42), but it may not fully take into account all of the variability induced by the uncertainties in the assessment of radon concentrations.