

Case-Control Study on Lung Cancer and Residential Radon in Western Germany

Lothar Kreienbrock,^{1,5} Michaela Kreuzer,^{1,6} Michael Gerken,¹ Gerlinde Dingerkus,² Jürgen Wellmann,¹ Gert Keller,³ and H. Erich Wichmann^{1,4}

In a 1990–1996 case-control study in western Germany, the authors investigated lung cancer risk due to exposure to residential radon. Confirmed lung cancer cases from hospitals and a random sample of community controls were interviewed by trained interviewers regarding different risk factors. For 1 year, alpha track detectors were placed in dwellings to measure radon gas concentrations. The evaluation included 1,449 cases and 2,297 controls recruited from the entire study area and a subsample of 365 cases and 595 controls from radon-prone areas of the basic study region. Rate ratios were estimated by using conditional logistic regression adjusted for smoking and for asbestos exposure. In the entire study area, no rate ratios different from 1.0 were found; in the radon-prone areas, the adjusted rate ratios for exposure in the present dwelling were 1.59 (95% confidence interval (CI): 1.08, 2.27), 1.93 (95% CI: 1.19, 3.13), and 1.93 (95% CI: 0.99, 3.77) for 50–80, 80–140, and >140 Bq/m³, respectively, compared with 0–50 Bq/m³. The excess rate ratio for an increase of 100 Bq/m³ was 0.13 (–0.12 to 0.46). An analysis based on cumulative exposure produced similar results. The results provide additional evidence that residential radon is a risk factor for lung cancer, although a risk was detected in radon-prone areas only, not in the entire study area. *Am J Epidemiol* 2001;153:42–52.

case-control studies; lung neoplasms; radon; smoking

Studies on underground miners show an increased lung cancer risk after exposure to radon and its progeny (1). These studies also suggest that exposure to residential radon may contribute to the incidence of lung cancer in the general population. It has been estimated that 4–12 percent of all lung cancers in Germany could be due to indoor radon (2). This finding has been confirmed by more recent estimates (7 percent) (3).

Direct epidemiologic investigations of the population have been conducted in New Jersey (4); China (5); south

Finland (6, 7); Stockholm, Sweden (8); Sweden nationwide (9); Canada (10); Missouri (11); Finland nationwide (12, 13); and southwest England (14). While an effect could not be observed in China, Canada, or Missouri, a slight effect was found in New Jersey; south Finland; Stockholm, Sweden; Finland nationwide; and England. The Swedish nationwide study showed a strong relation. Overall, in a meta-analysis of the results of the first eight studies mentioned above (4–11), the authors found an exposure-disease relation between residential radon and lung cancer in the general population and that the magnitude of the relation was close to the results from extrapolations from the studies of miners (15).

To investigate the association between residential radon and lung cancer based on German living conditions, we conducted a case-control study in parts of western Germany.

MATERIALS AND METHODS

Study design

The investigation took place in several areas of western Germany. The definition of the study area was based on administrative districts in relation to a radon survey conducted in houses in the 1980s (2) and on the underlying geology (16). This definition yielded the three radon-prone matching areas of Eifel, Westerwald/Hunsrueck, and Upper Palatinate/Lower Bavaria, which can be characterized as rural and as having a low population density and lung cancer incidence.

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Abbreviations: CI, confidence interval; SSNTD, solid-state nuclear track detector.

¹ Institute of Epidemiology, GSF-National Research Center for Environment and Health, Neuherberg, Federal Republic of Germany.

² Department of Labour Safety and Environmental Medicine, University of Wuppertal, Wuppertal, Federal Republic of Germany.

³ Biophysics Unit, Saar University Homburg, Homburg, Federal Republic of Germany.

⁴ Department of Epidemiology, Ludwig-Maximilians-University Munich, Munich, Federal Republic of Germany.

⁵ Present address: Institute for Biometry, Epidemiology and Information Processing, Hannover School of Veterinary Medicine, Hannover, Federal Republic of Germany.

⁶ Present address: Federal Office of Radiation Protection, Institute of Radiation Hygiene, Neuherberg, Federal Republic of Germany.

Correspondence to Dr. Lothar Kreienbrock, Institute for Biometry, Epidemiology and Information Processing, Hannover School of Veterinary Medicine, Buenteweg 2, 30559 Hannover, Federal Republic of Germany (e-mail: lothar.kreienbrock@tiho-hannover.de).

To ensure the necessary study size (17), it was not possible to restrict the study to the few sparsely populated, radon-prone areas. Therefore, we also included more densely populated urban areas in which the potential exposure to radon is, on average, low. Final matching regions were defined during case enrollment on the basis of frequency matching (18).

Cases were recruited in nine hospitals from October 1990 to October 1995 and were eligible if 1) they currently resided in the study region, 2) they had lived in Germany since 1965, 3) they were familiar with the German language, 4) they were not older than age 75 years, 5) they were interviewed within 3 months after the first diagnosis, 6) the diagnosis of lung cancer as a primary tumor was confirmed histologically or cytologically by the hospital's pathologist, 7) there was no initial evidence of tuberculosis, and 8) they had never worked in the SDAG Wismut uranium mining industry. The response rate for eligible cases was 79 percent.

To ensure that histologic subtypes were classified uniformly, the original pathologic material was also reviewed blinded by two reference pathologists, one for the histologic and one for the cytologic material. This material was obtained for about 75 percent of all cases' tumors. The following subtypes were considered: small-cell carcinoma, squamous-cell carcinoma, adenocarcinoma, and other bronchial cancers.

Population controls were interviewed from October 1990 to March 1996 and were frequency-matched to cases on gender, age (six 5-year classes), and 13 matching regions (including rural, suburban, and urban areas). Inclusion criteria 1–4 and 8 were the same as those for the cases. Two strategies for randomly selecting population controls were used. One was to take a random sample from the mandatory registries of residents of the reference communities. In regions that had only a few expected cases and a low population density, controls were selected by using a random digit dialing technique modified for the German telephone system (19). Each control was personally interviewed at home. Response rates differed in terms of area and strategy. Overall, the rates were 38 percent for the entire study area and 46 percent for the radon-prone matching areas.

Interviews were conducted in person by trained staff. A standardized questionnaire was used to ascertain demographic characteristics as well as extensive details on residential history, housing conditions, house alterations, and ventilation practices in all homes occupied during the last 35 years before interview. Furthermore, questions on active and passive smoking, occupational exposure, dietary habits, and personal and family medical histories were asked.

Smoking was quantified on the basis of information obtained from the questionnaire. Lifelong smoking history was documented for periods of similar smoking habits for cigarette smoking and other types of tobacco use. Subjects were defined as smokers if they had ever smoked regularly (at least one cigarette per day, four cigarillos per week, or three cigars or three pipes per week) for at least 6 months. Active smokers and former smokers were summarized as smokers and were compared with lifelong nonsmokers. In

the analysis, years of smoking, age at which smoking started, average cigarettes smoked per day, pack-years of smoking, and time since cessation were considered.

For all participants, occupational exposures were evaluated on the basis of job-specific questionnaires, and the life-long history of all jobs and industries was coded. For the present analysis, only exposure to asbestos (ever/never) was considered; more detailed occupational analyses are described elsewhere (20).

Radon measurements and exposure assessment

Radon concentrations were measured in the present home and in the previous homes of participants, which were identified via telephone and mandatory registries. Solid-state nuclear track detectors (SSNTDs) for long-term measurements were used for 1 year. The detectors were exposed in the living room and the bedroom of a participant's dwellings.

The SSNTD consists of a polycarbonate foil (Makrofol; Bayer AG, Leverkusen, Germany) inside a KfK (Kernforschungszentrum Karlsruhe)-type capsule. Radon enters the capsule through a glass fiber filter and irradiates the foil by alpha radiation. The alpha particles of the short-lived progeny of ^{222}Rn (^{218}Po and ^{214}Po) are registered as well. After exposure, the latent alpha tracks are enlarged in two steps by chemical and electrochemical etching to visible tracks (21). The track density of the foils is measured after 1 year of exposure to determine the radon concentration. Concentrations of more than 400 Bq/m³ require a shorter exposure time. Relevant houses were identified via spot measurement conducted with activated charcoal detectors (22–24), and several SSNTDs, equally distributed over the year, were exposed. In this situation, the 1-year radon concentration was calculated as a time-weighted average of the submeasurements.

Radon exposure was quantified in two ways. First, a weighted average of the radon concentrations in the living room and the bedroom of the present home was calculated, taking into account the proportion of time spent in each room. Information on the amount of time spent in each room was collected individually for each subject. If the bedroom measurement was missing, the living room measurement was substituted and was multiplied by a correction factor of 0.94 (given by the median ratio of bedroom and living room measurements), and vice versa. This exposure was measured in terms of Bq/m³.

The second approach considered the average cumulative exposure per year 5–15 years before interview. This exposure window was identified before analysis as the most relevant time interval with respect to lung cancer risk due to radon (1, 25). Here, the measurement in the present home was supplemented by measurements from the previous homes. Changes due to alteration of the house or different ventilation practices of the study participants and the present inhabitants were considered by using a correction factor developed in a multivariate model (26). This exposure was expressed in terms of Bq/m³ · a per year.

Study subjects and homes measured

In the entire study area, 2,294 confirmed lung cancer cases and 2,488 population controls were interviewed. A subsample of 584 cases and 645 controls was living in the radon-prone matching areas initially introduced as the basic study region. To ensure the quality of the radon assessment, the present analysis was restricted to subjects for whom questionnaire information and SSNTD information regarding the current home were complete. Subjects were excluded if 1) they had spent less than 25 percent of their time in their homes (96 cases, 44 controls), 2) SSNTD measurements had not been conducted for 1 year $\pm$ 2 months (to avoid seasonal effects) (135 cases, 59 controls), 3) SSNTD measurements were incomplete (592 cases, 82 controls), or 4) smoking history was incomplete (22 cases, 6 controls). These criteria reduced the sample size to 1,449 cases and 2,297 controls in the entire study region and 365 cases and 595 controls in the radon-prone matching areas.

Detailed information was collected on residences that had been occupied during the 35 years before interview. Cases and controls had not moved frequently. For the last 35 years, the entire study area included 3,971 homes (50,700 residential years) for cases and 6,787 homes (80,344 residential years) for controls. On average, subjects in all groups had occupied their current residences for 23 years. In the entire study area, 31,373 residential years (62 percent within 35 years) for the cases and 49,181 residential years (61 percent within 35 years) for the controls were covered by the current home.

With respect to cumulative radon exposure 5–15 years before interview, 1,865 homes of cases (14,490 residential years within the 5–15 years before interview) and 3,004 homes of controls (22,970 residential years) remained. Only those subjects for whom the time window covered by radon measurements was complete were included in this analysis, thus reducing the database for this analysis to 1,023 cases and 1,626 controls. A total of 10,230 residential years for cases and 16,590 residential years for controls yielded a measurement response rate of 71 percent for cases and 72 percent for controls.

Statistical methods

Rate ratios and asymptotic 95 percent confidence intervals were calculated via conditional logistic regression, in which matching was considered by strata for gender, age (in six classes), and 13 matching areas. Exposure to domestic radon was treated as a categorical variable with cutpoints at 50, 80, and 140 Bq/m³. A linear trend was calculated by treating radon exposure as a continuous variate and determining an excess rate ratio per additional exposure of 100 Bq/m³ by calculating the odds ratio per 100 Bq/m³ and subtracting 1. Cigarette smoking was considered as “log(pack-years + 1)” and “years since quitting” in four categories (current smoker/quit less than 2 years ago, quit 2–5 years ago, quit 5–10 years ago, quit more than 10 years ago). Smoking of other products was ignored for cigarette smokers and was binary coded for non-cigarette smokers.

Possible occupational confounding was linked to dichotomous exposure to asbestos (ever exposed vs. never exposed). Statistical analysis for the risk analysis was carried out by using the PHREG procedure in SAS software, release 6.09 (27).

RESULTS

The demographic characteristics of the population analyzed are outlined in table 1. More than 80 percent of the cases were men. The average ages of the cases were 61 years for men and 58 years for women. Among men, squamous-cell carcinoma was the most frequent tumor type; among women, adenocarcinoma was much more frequent. Years in school is the best proxy for social status in epidemiologic studies conducted in Germany and was defined in our study as the highest school degree earned. Clear differences were observed between the cases and controls in this respect. These characteristics were distributed similarly in the entire study region and in the radon-prone matching areas.

Table 2 shows the characteristics of possible confounding factors such as smoking history and occupational asbestos exposure. Only 2 percent of the male cases (23 study subjects) were lifelong nonsmokers in contrast to 31 percent of the female cases. Among controls, the proportions of lifelong nonsmokers were 23 percent for men and 60 percent for women. These smoking patterns resulted in strong exposure-response associations in the risk analysis. For men, the rate ratios adjusted for asbestos exposure were 5.5 (95 percent confidence interval (CI): 3.4, 8.9), 16.7 (95 percent CI: 10.8, 25.9), 21.0 (95 percent CI: 13.4, 32.9), and 21.9 (95 percent CI: 13.6, 35.2) for an average daily quantity of 1–10, 11–20, 21–30, and more than 30 cigarettes, respec-

TABLE 1. Demographic characteristics of the population studied to investigate the association between residential radon and lung cancer, western Germany, 1990–1996

Characteristic	Cases (n = 1,449)		Controls (n = 2,297)	
	No.	%	No.	%
Gender				
Men	1,214	83.4	1,865	81.2
Women	235	16.6	432	18.8
Histologic review (men)				
Small-cell carcinoma	256	21.1	NA*	NA
Squamous-cell carcinoma	494	40.7	NA	NA
Adenocarcinoma	387	31.9	NA	NA
Other carcinoma	77	6.3	NA	NA
Histologic review (women)				
Small-cell carcinoma	50	21.3	NA	NA
Squamous-cell carcinoma	55	23.4	NA	NA
Adenocarcinoma	109	46.4	NA	NA
Other carcinoma	21	8.9	NA	NA
Years in school†				
No formal qualification	17	1.2	18	0.8
≤8	1,195	82.5	1,402	61.0
9–10	135	9.3	392	17.1
11–12	18	1.2	98	4.3
≥13	79	5.5	385	16.8
Other	5	0.3	2	0.1

* NA, not applicable.

† For controls, percentages do not total 100 because of rounding.

TABLE 2. Characteristics and risks of possible confounding factors in the population studied to investigate the association between residential radon and lung cancer, western Germany, 1990–1996

Characteristic	Men						Women					
	Cases (n = 1,214)		Controls (n = 1,865)		RR*	95% CI*	Cases (n = 235)		Controls (n = 432)		RR	95% CI
	No.	%	No.	%			No.	%	No.	%		
Smoking history												
Lifelong nonsmoker	23	1.9	434	23.3	1.0		72	30.6	260	60.2	1.0	
Cigarette smoker only	902	74.3	1,054	56.5	15.8	10.2, 24.3	163	69.4	169	39.1	3.3	2.3, 4.7
Mixed smoker†	280	23.1	312	16.7	15.9	10.1, 25.1	0	0	3	0.7	NR*	
Pipe, etc., smoker only	9	0.7	65	3.5	5.9	1.2, 6.1	0	0	0	0	NR	
Cigarette pack-years												
Lifelong nonsmoker	23	1.9	434	23.3	1.0		72	30.6	260	60.2	1.0	
0–<20	208	17.1	659	35.3	5.9	3.8, 9.3	55	23.4	124	28.7	1.4	0.9, 2.2
20–<40	475	39.1	460	24.7	19.0	12.2, 29.6	69	29.4	39	9.0	5.8	3.5, 9.6
≥40	499	41.1	247	13.2	37.0	23.5, 58.2	39	16.6	9	2.1	13.6	6.1, 30.8
Years since quitting smoking												
Lifelong nonsmoker	23	1.9	434	23.3	1.0		72	30.6	260	60.2	1.0	
≤2 and current	825	68.0	512	27.5	29.7	19.2, 45.9	133	56.6	81	18.8	5.5	3.6, 8.2
2–≤5	91	7.5	77	4.1	20.5	12.1, 34.7	5	2.1	11	2.5	NR	
5–≤10	82	6.8	124	6.6	11.9	7.1, 19.8	7	3.0	16	3.7	1.9	0.7, 5.1
>10	184	15.2	653	35.0	4.5	2.8, 7.1	18	7.7	64	14.8	0.9	0.7, 5.1
Occupational asbestos exposure												
Never	842	69.4	1,495	80.2	1.0		229	97.4	432	100	1.0	
Ever	372	30.6	370	19.8	1.7	1.4, 2.0	6	2.6	0	0	NR	

* RR, rate ratio (adjusted); CI, confidence interval (asymptotic); NR, not reported because of fewer than 10 cases in the reference group or fewer than 20 cases and controls in the category.

† Smoker of cigarettes, a pipe, and other forms of tobacco simultaneously.

tively, compared with never smokers. For women, these ratios were 1.3 (95 percent CI: 0.8, 2.3), 4.0 (95 percent CI: 2.6, 6.2), 6.8 (95 percent CI: 3.5, 13.3), and 9.4 (95 percent CI: 2.7, 32.2), respectively. Similar patterns were found for other quantifications of smoking exposure in both the entire study region and the radon-prone matching areas.

Occupational asbestos exposure was found for men only (30.6 percent of the cases, 19.8 percent of the controls), yielding a smoking-adjusted rate ratio of 1.7 (95 percent CI: 1.4, 2.0). Distribution of this risk factor in the entire study region and in the radon-prone matching areas was very similar.

The observed radon concentrations in the present dwellings (occupancy-weighted average of the 1-year measurements in the living room and bedroom) showed a log-normal distribution. In the entire study area, the mean concentrations were 49 Bq/m³ for cases and 50 Bq/m³ for controls; in the radon-prone matching areas, the concentrations were 67 and 60 Bq/m³, respectively (table 3).

In the entire study area, cases spent an average of 7.9 hours in the bedroom and 7.0 hours in the main living room. For controls, these averages were 7.8 and 7.1 hours, respectively. When holidays and other periods of absence from home were considered, both cases and controls spent 57 percent of their time at home. All these numbers were slightly higher in the radon-prone matching areas.

Lung cancer risks due to the radon concentration in the last dwelling are presented in table 4. For the entire study area, no increased lung cancer risk was evident from any result obtained from logistic regression analysis. In contrast, an exposure-response relation was observed for the radon-prone matching areas. The rate ratio was increased in all cat-

TABLE 3. Radon concentrations (Bq/m³)* in present dwellings of the population studied to investigate the association between residential radon and lung cancer, western Germany, 1990–1996

Concentration	Entire study area		Radon-prone matching areas	
	Cases (n = 1,449)	Controls (n = 2,297)	Cases (n = 365)	Controls (n = 595)
Minimum	8	8	10	11
Maximum	760	922	455	922
Median	40	40	52	46
Mean	49	50	67	60
Standard deviation	41	47	50	66
Coefficient of variation (%)	85	95	75	110
Geometric mean	40	41	55	48
Geometric standard deviation	2	2	2	2

* Individual occupancy-weighted average of living and bedroom measurements.

egories, and the increase was stronger after adjustment. The adjusted rate ratios referring to the exposure in the last dwelling were 1.59 (95 percent CI: 1.08, 2.27), 1.93 (95 percent CI: 1.19, 3.13), and 1.93 (95 percent CI: 0.99, 3.77) for 50–80, 80–140, and more than 140 Bq/m³, respectively, compared with 0–50 Bq/m³. The adjusted linear trend test showed an elevated excess rate ratio of 0.13 for an increase of 100 Bq/m³ in the radon concentration. This trend was not statistically significant at the 5-percent level.

TABLE 4. Relative lung cancer risk due to residential radon in western Germany, according to the radon concentration* in the last dwelling, 1990–1996†

Radon concentration (Bq/m ³)	Entire study area					Radon-prone matching areas				
	Cases		Controls		RR‡§ (95% CI)†	Cases		Controls		RR¶ (95% CI)
	No.	%	No.	%		No.	%	No.	%	
0–50	1,022	70.5	1,542	67.1	1.00	178	48.8	345	58.0	1.00
50–80	284	19.6	512	22.3	0.84 (0.71 to 1.00)	104	28.5	156	26.2	1.29 (0.94 to 1.76)
80–140	108	7.5	178	7.7	0.87 (0.67 to 1.14)	58	15.9	65	10.9	1.66 (1.11 to 2.50)
>140	35	2.4	65	2.8	0.81 (0.52 to 1.25)	25	6.8	29	4.9	1.61 (0.91 to 2.88)
ERR‡	NA‡	NA	NA	NA	–0.12 (–0.26 to 0.04)	NA	NA	NA	NA	0.15 (–0.08 to 0.44)
					–0.02 (–0.18 to 0.17)					0.13 (–0.12 to 0.46)

* Living-room measurement substituted for bedroom measurement if the latter was missing, and vice versa; measurement was adjusted for dwelling conditions and time-weighted means of living and bedroom measurements (Bq/m³).

† Some percentages do not total 100 because of rounding.

‡ RR, rate ratio; CI, confidence interval; ERR, excess rate ratio as odds ratio – 1 per 100 Bq/m³; NA, not applicable.

§ Unadjusted odds ratio matched on age, gender, and region.

¶ Adjusted for smoking (log(pack-years + 1), no. of years since quitting), and asbestos (exposed vs. nonexposed).

Regarding cumulative annual radon exposure during the last 5–15 years (table 5), no elevated rate ratios were found for the entire study area either, although these ratios were slightly higher than those shown in table 4. For the radon-prone matching areas, again a positive exposure-response relation was observed that was slightly higher than that based on the present homes. The adjusted rate ratios referring to cumulative exposure during the last 5–15 years before interview were 1.67 (95 percent CI: 1.04, 2.69), 1.55 (95 percent CI: 0.83, 2.90), and 2.60 (95 percent CI: 1.38, 4.93) for 20–40, 40–60, and more than 60 Bq/m³ · a per year, respectively, compared with 0–20 Bq/m³ · a per year. The adjusted linear trend yielded an excess rate ratio of 0.09 for an increase of 50 Bq/m³ · a per year in cumulative exposure. Again, this excess was not statistically significant at the 5-percent level.

Risk analysis separated by histopathologic subtype showed similar results. For no subtype was an effect found in the entire study area; for all subtypes, there was a tendency for elevated rate ratios in the radon-prone matching areas. Most of these rate ratios were not statistically significant because of small numbers. The strongest effect was observed for small-cell carcinoma (table 6). The highest exposure category (>140 Bq/m³) was associated with a 1.5-fold (95 percent CI: 0.7, 3.2) increased lung cancer risk in the entire study area and a 3.4-fold (95 percent CI: 1.3, 8.7) increased lung cancer risk in the radon-prone matching areas.

DISCUSSION

Our case-control study on residential radon and lung cancer in western Germany was based on 1,449 cases and 2,297 controls for whom information on radon measurements in their current homes was complete. Study subjects were enrolled in areas in which elevated radon concentrations could be expected and in surrounding areas with low expected radon concentrations. Two principal results were found. In the entire study area, no rate ratios were significantly different from 1.0; in the subsample of radon-prone matching areas, an influence of exposure to radon on lung cancer risk was observed. Smoking and exposure to asbestos are the predominant risk factors for lung cancer. An association was observed in both the entire study region and the radon-prone matching areas, where risk patterns were similar.

Study design and risk assessment

This study was conducted as a 1:1 case-control study with hospital-based cases and population-based controls. Radon exposure was assessed via 1-year measurements of radon gas concentrations in the current and previous homes of study subjects. The basic risk analysis was conducted as a conditional logistic regression, and categorized radon exposures were adjusted for smoking and for occupational exposure to asbestos. The study design is in agreement with international recommendations on studies of the relation between radon and lung cancer (28, 29).

Nevertheless, because of the small risk from radon compared with smoking, general uncertainty probably influ-

TABLE 5. Relative lung cancer risk due to residential radon in western Germany, according to cumulative radon* exposure during the last 5–15 years before interview, 1990–1996†

Cumulative radon exposure (Bq/m ³ · a/year)	Entire study area						Radon-prone matching areas					
	Cases		Controls		RR‡,§ (95% CI‡)	RR¶ (95% CI)	Cases		Controls		RR§ (95% CI)	RR¶ (95% CI)
	No.	%	No.	%			No.	%	No.	%		
0–20	459	44.9	710	43.7	1.00	1.00	56	22.8	122	30.2	1.00	1.00
20–40	410	40.1	621	38.2	1.03 (0.86 to 1.24)	1.16 (0.94 to 1.43)	109	44.3	170	42.1	1.52 (1.01 to 2.69)	1.67 (1.04 to 2.69)
40–60	87	8.5	184	11.3	0.73 (0.54 to 0.99)	0.82 (0.58 to 1.16)	40	16.3	66	16.3	1.41 (0.83 to 2.90)	1.55 (0.83 to 2.90)
>60	67	6.5	111	6.8	0.96 (0.67 to 1.36)	1.21 (0.81 to 1.81)	41	16.7	46	11.4	2.05 (1.18 to 3.56)	2.60 (1.38 to 4.93)
ERR‡	NA‡	NA	NA	NA	–0.09 (–0.22 to 0.06)	–0.03 (–0.18 to 0.14)	NA	NA	NA	NA	0.07 (–0.13 to 0.32)	0.09 (–0.14 to 0.38)

* Cumulative radon, living-room measurement substituted for bedroom measurement if the latter was missing, and vice versa; measurement was adjusted for dwelling conditions and time-weighted means of living and bedroom measurements accumulated 5–15 years before interview and was averaged per year (Bq/m³ · a per year).

† Some percentages do not total 100 because of rounding.

‡ RR, rate ratio; CI, confidence interval; ERR, excess rate ratio as odds ratio – 1 per 50 Bq/m³ · a per year; NA, not applicable.

§ Unadjusted odds ratio matched on age, gender, and region.

¶ Adjusted for smoking (log(pack-years + 1), no. of years since quitting), and asbestos (exposed vs. nonexposed).

TABLE 6. Relative risk for small-cell carcinoma lung cancer due to residential radon in western Germany, according to the radon concentration* in the last dwelling, 1990–1996†

Radon (Bq/m ³ /year)	Entire study area						Radon-prone matching areas					
	Cases		Controls		RR‡,§ (95% CI‡)	RR¶ (95% CI)	Cases		Controls		RR§ (95% CI)	RR¶ (95% CI)
	No.	%	No.	%			No.	%	No.	%		
0–50	215	69.6	1,340	67.2	1.00	1.00	52	51.5	300	57.9	1.00	1.00
50–80	59	19.1	440	22.1	0.84 (0.61 to 1.15)	0.99 (0.69 to 1.42)	25	24.8	133	25.7	1.20 (0.71 to 2.04)	1.35 (0.72 to 2.53)
80–140	24	7.8	156	7.8	0.90 (0.56 to 1.46)	1.01 (0.59 to 1.74)	14	13.9	60	11.6	1.49 (0.75 to 2.97)	1.55 (0.70 to 3.46)
>140	11	3.6	58	2.9	1.12 (0.56 to 2.23)	1.48 (0.69 to 3.18)	10	9.9	25	4.8	2.42 (1.07 to 5.45)	3.41 (1.33 to 8.73)
ERR‡	NA‡	NA	NA	NA	–0.06 (–0.28 to 0.23)	–0.01 (–0.23 to 0.27)	NA	NA	NA	NA	0.16 (–0.11 to 0.51)	0.11 (–0.17 to 0.47)

* Living-room measurement substituted for bedroom measurement if the latter was missing, and vice versa; measurement was adjusted for dwelling conditions and time-weighted means of living and bedroom measurements (Bq/m³).

† Some percentages do not total 100 because of rounding.

‡ RR, rate ratio; CI, confidence interval; ERR, excess rate ratio as odds ratio – 1 per 100 Bq/m³; NA, not applicable.

§ Unadjusted odds ratio matched on age, gender, and region.

¶ Adjusted for smoking (log(pack-years + 1), no. of years since quitting), and asbestos (exposed vs. nonexposed).

enced the power of this study. Therefore, a series of sensitivity analyses was conducted to review the results from both the entire study region and the radon-prone matching areas.

The cutpoints of 50, 80, and 140 Bq/m³ were chosen for the calculations before the analysis was conducted. These cutpoints are related to other studies or action levels. The average radon level in Germany is 50 Bq/m³ (2); 80 and 140 Bq/m³ were used in the Swedish nationwide study (9). In addition, 140 Bq/m³ is the US action level. Cutpoints above this level were omitted because of small numbers. In the entire study region, these cutpoints yielded a disproportional distribution of the study subjects within the categories; approximately 70 percent of the study subjects were in the reference category, which decreased the power of the risk analysis.

In a sensitivity analysis, other models were fitted by using different external cutpoints or by using percentiles. The results of these analyses differed with respect to the reference chosen. Reference points of less than 50 Bq/m³ yielded more or less uniform distributions of the study subjects within the categories; therefore, we observed an increase in statistical power. When tertiles, quartiles, quintiles, or a logarithmic cutpoint approach (25, 50, 100, 200 Bq/m³ (14)) was used, the adjusted rate ratios increased even for the entire study region; some, but not most, were statistically significant at the 5-percent level.

A further loss of power could have been introduced by exposure assessment. Radon measurement in a subject's current home was one assessment method used. Current homes were occupied for 23 years on average, a finding in line with those from other studies conducted in Europe (8, 9, 12, 14). Current homes therefore account for a huge amount of lifetime residential exposure. In addition, our measurements were conducted with respect to study subjects' real living habits, which increased the precision of exposure assessment. Moreover, calculation of average cumulative exposure 5–15 years before interview was a second assessment method used, which additionally included individual occupancy times. This time window was selected as the most relevant for analysis on the basis of the risk models constructed for the studies of miners (1). Other time windows chosen did not change the results. This finding indicates that in our study, the method of exposure assessment used was less important.

Confounding

Confounding was controlled for by considering all possible risk factors. Lifelong smoking exposure was included in the analysis, including detailed information on intensity and duration within periods of similar smoking habits, occupational exposure to asbestos, and the matching factors of gender, age, and area. Further adjustment was tested in terms of additional occupational exposure, environmental tobacco smoke exposure, nutrition, and social status. Since these factors did not change the radon estimates, they were omitted from the final risk model.

Smoking was identified as the most relevant risk factor in the etiology of lung cancer. In addition, occupational expo-

sure to asbestos was identified as a risk for men. The risk patterns observed were comparable to those found in other studies, especially in Germany (30). A negative confounding effect of smoking on the radon risk was observed. Adjustment for occupational exposure to asbestos did not change the results of the radon risk assessment. While a confounding effect for occupational exposure may not be expected, several earlier studies showed similar results for smoking habits (8, 9, 12). These findings were present in both the entire study region and the radon-prone matching areas, where smoking risks were very similar. Taking into account that regional matching was included in the analysis, it is unlikely that the study results reflected a confounding bias.

Selection

Some potential methodological problems in our study concern the recruitment of cases and the low response rates among controls. Currently, there is no overall cancer registry in Germany. Therefore, in our study, patients had to be selected via hospitals. To estimate the coverage, we compared the average number of lung cancer cases per year enrolled from the study hospitals in the subregion of Saarland with data from the Saarland cancer registry by using the average number of lung cancers per year. The coverage was about 50 percent. Since we had no information on the possible risk factors of the overall lung cancer cases, the representativeness of our cases was not measurable. However, the age distribution of subjects less than age 75 years was similar to that in the cancer registry. In case recruitment, a refusal rate of 21 percent overall indicates that a selection bias for cases was unlikely.

Of the cases interviewed, an additional 37 percent were not selected for analysis because radon measurements were missing or incomplete. This factor could possibly have introduced a bias if the reasons for failure were linked to radon exposure. However, most information was incomplete because patients were very ill or cases died during the measurement campaign, and these figures were very similar in both the entire study region and the radon-prone matching areas.

Compared with other studies, the response rate for controls was low in our study. We therefore analyzed whether this finding could explain the different results in the entire study area and the radon-prone matching areas. For a random sample of 250 nonresponders, a telephone interview was conducted (19). The response rate for this interview was also low (21 percent). Nevertheless, the results of this analysis were close to those for other population samples in epidemiologic studies in Germany (19). Better-educated people (social status), younger people, and people in rural areas participated more frequently than others did. Since social status was controlled for by accounting for smoking, and age was controlled for by matching, the response pattern may not have influenced the results, which is documented by similar risks for smoking and occupational exposures in the entire study region and in the radon-prone matching areas and by comparison of the control sample with 1995 census data from the Federal Office of Statistics (31).

However, this finding was not true for the radon exposures. Although general patterns in the housing characteristics of the responders and the nonresponders did not differ, differences in the responses from controls in rural and urban areas were observed. Thus, nonexposed controls in urban areas were underrepresented, mainly because people of lower social classes lived in flats that had low radon concentrations. This finding may have contributed to a bias toward the null value in the entire study region.

Information

In many case-control studies on lung cancer risk due to radon, cases are recruited via cancer registries (9–12). With this approach, complete coverage of cases in the study area is possible. However, because of the poor lung cancer prognosis, most cases have already died before interviews and radon measurements are conducted. Thus, most of the information obtained depends on cases' next of kin as well as on measurements in homes of other persons. This factor may introduce a misclassification bias resulting from uncertainties in remembering questionnaire details. In contrast, in our study, this problem was unlikely because personal interviews were conducted with the study subjects, which increased precision.

In addition, much effort was invested in quantifying individual exposure appropriately. Radon detectors were installed for 1 year in both the living room and the bedroom.

A detailed analysis of the radon concentrations was performed, depending on the characteristics of the home and the ventilation practices (26). Thus, it was possible to adjust for differences in ventilation practices between study participants and the present inhabitants of participants' previous homes as well as for alterations such as different windows or a new heating system. Furthermore, time spent in the different rooms was taken into account, and individual occupancy factors were developed from questionnaire information.

In spite of these efforts to improve exposure assessment, uncertainty remained because of a small range of radon concentrations, especially in the entire study region. To explain the differences in risks observed in the entire study region and in the radon-prone matching areas, a sensitivity analysis was conducted by looking at special unfavorable dwelling conditions known to be related to an increase in residential radon concentrations in homes in western Germany (2). Seven sub-samples were considered, namely houses 1) in villages with fewer than 5,000 inhabitants, 2) built before 1900, 3) half timbered, 4) with a missing or partial basement, 5) with a basement floor of loam or natural stone, 6) with poorly insulated basements, and 7) with infrequently opened windows.

The cumulative frequency distributions for these subgroups showed a shift to higher exposures for cases already in the entire study area. This effect was even more pronounced in the radon-prone matching areas and in houses with more than one of these radon-relevant criteria (figures 1 and 2). A

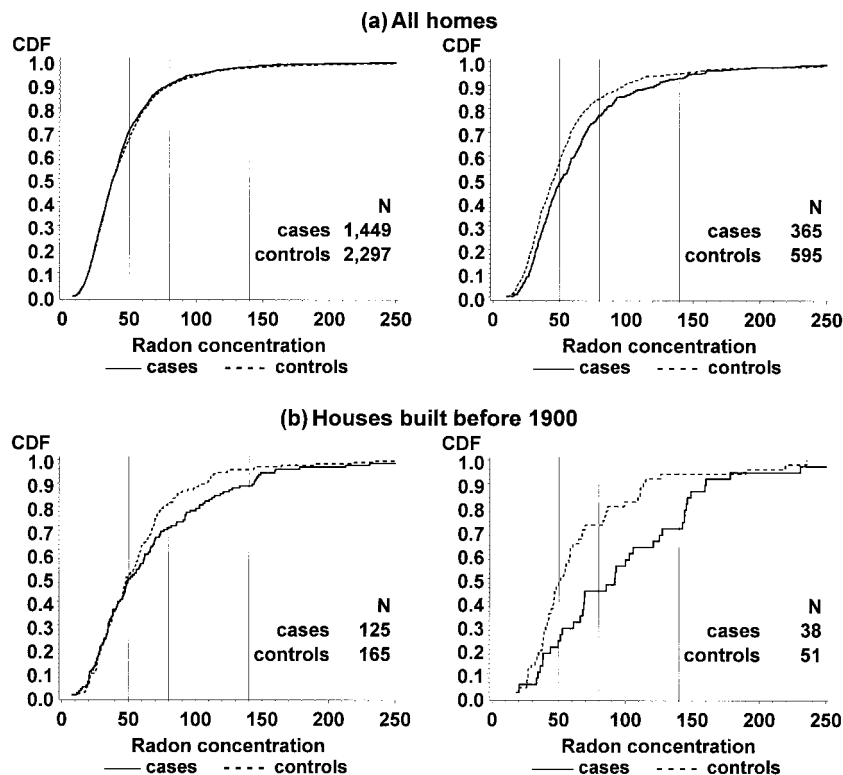


FIGURE 1. Cumulative frequency distribution (CDF) of radon concentration (Bq/m^3) for cases and controls in the radon study conducted in western Germany (1990–1996) in subpopulations of different house types: (a) all residences and (b) houses built before 1900; left column: entire study region; right column: radon-prone matching areas.

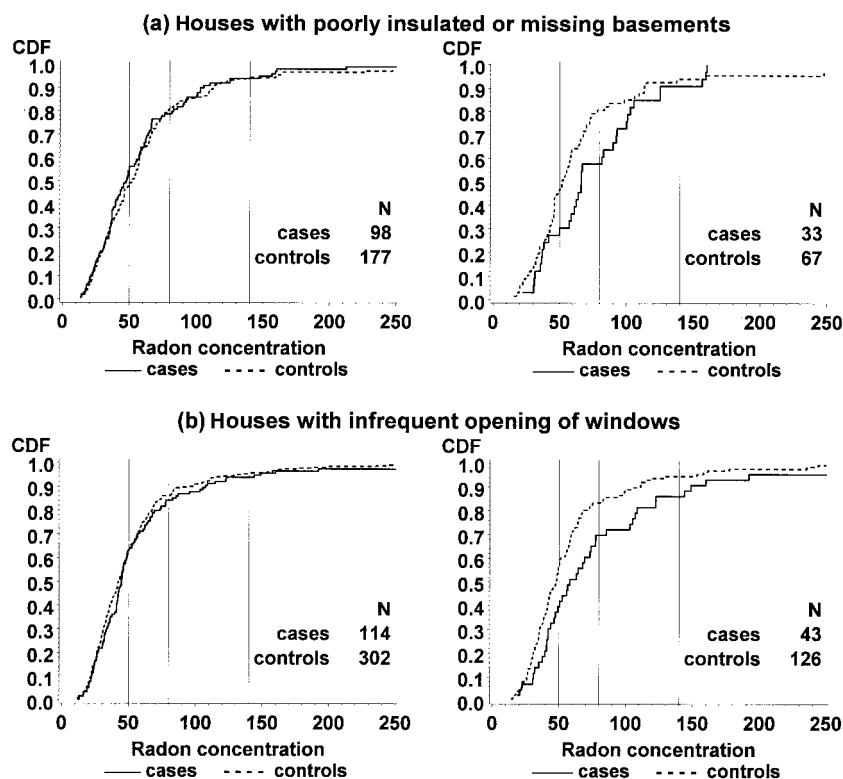


FIGURE 2. Cumulative frequency distribution (CDF) of radon concentration (Bq/m^3) for cases and controls in the radon study conducted in western Germany (1990–1996) in subpopulations of different house types: (a) houses with poorly insulated or missing basements and (b) houses with infrequent opening of windows; left column: entire study region, right column: radon-prone matching areas.

similar effect was described in the Swedish nationwide study (9), in which increased risks were observed for study subjects who slept with their windows closed, while study subjects who slept with their windows open seemed to have no risk.

A possible explanation for these results is the remaining inaccuracy of radon exposure assessment. This inaccuracy increases if the variation in exposure within the study population is low. It is indeed possible that adding a large number of subjects with low exposure would dilute and mask an effect, which could explain the difference in results between the entire study area and the radon-prone areas. The same argument holds for the subgroups that had radon-relevant housing characteristics or for the result found in the Swedish nationwide study (9) of increased risk associated with sleeping with closed windows.

Our study, which included a large number of homes with low exposure and a small variation in radon concentrations in the entire study area, clearly illustrates the problem of exposure misclassification related to measurement error. Under normal conditions, a “regression toward the null” is observed; that is, the observable effect is partly or completely lost by random misclassification (32, 33). This may be one reason that, in most of the radon studies published thus far, no significant exposure-response associations have been found. Reanalysis of the Swedish nationwide study (34) and the study in southwest England (14) showed

increased risk estimates if one corrected for random misclassification, which supports this argument.

Comparison with other studies

A basis for comparing the results of this study with those of other studies is given by the meta-analysis (15) in which eight important case-control studies from the United States (4, 11), Canada (10), Sweden (8, 9), Finland (6, 12), and China (5) were analyzed. A total of 4,263 cases and 6,612 controls were considered. A significantly increased risk was found in the south Finland study (6), the two Swedish studies (8, 9), and the New Jersey study (4). The meta-analysis showed a statistically significant trend for a risk that increased with exposure. The excess relative risk for an increase of 100 Bq/m^3 was 0.09 (95 percent CI: 0.01, 0.19). Because the results of the Finnish nationwide study were corrected to an excess relative risk of 0.11 (95 percent CI: -0.14 to 0.42) (13), the results of the meta-analysis must be corrected slightly upward. The recently published study in southwest England (14) showed an excess relative risk of 0.08 (95 percent CI: -0.03 to 0.20).

Compared with these findings, our study found no trend in the entire study area. However, in the radon-prone matching areas, the corresponding excess relative risks were 0.13 (95 percent CI: -0.08 to 0.44) for the exposure assessment

in which only the last residence was used and 0.09 (95 percent CI: -0.14 to 0.28) for the exposure assessment in which the average cumulative exposure during the last 5–15 years before interview was used. Therefore, the results for the radon-prone matching areas are in very good agreement with the results of the meta-analysis (15) and especially with the results of the individual European studies. In addition, these results are close to extrapolations of the pooled analysis of the 11 studies of miners (1), in which an excess relative risk of 0.08 (95 percent CI: 0.00, 0.13) was found for 100 Bq/m³.

Conclusion

In summary, this case-control study on the etiology of lung cancer conducted in parts of western Germany found no risk associated with exposure to residential radon in the entire study region, while a radon risk was observed in a subsample of radon-prone matching areas. These results are within the range of those from the available case-control studies on indoor radon and the corresponding extrapolations from data on miners, which suggests that exposure to residential radon contributes in a relevant manner to lung cancer risk in the general population. In contrast, cigarette smoking is clearly the predominate risk factor for lung cancer in the German population; for males, prior asbestos exposure also is relevant.

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