



Exposure to Residential Radon and Lung Cancer in Spain: A Population-based Case-Control Study

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Although high radon concentrations have been linked to increased risk of lung cancer by both experimental studies and investigations of underground miners, epidemiologic studies of residential radon exposure display inconsistencies. The authors therefore decided to conduct a population-based case-control study in northwest Spain to determine the risk of lung cancer associated with exposure to residential radon. The study covered a total of 163 subjects with incident lung cancer and a population sample of 241 cancer-free subjects since 1992–1994. Odds ratios for radon were estimated using logistic regression adjusted for sex, age, lifetime tobacco use, family history, and habitat. The adjusted odds ratios for the second, third, and fourth quartiles of radon (breakpoints: 37.0, 55.2, and 148.0 Bq/m³) were 2.73 (95% confidence interval (CI): 1.12, 5.48), 2.48 (95% CI: 1.29, 6.79), and 2.96 (95% CI: 1.29, 6.79), respectively. An additive synergic effect between radon and tobacco was found. The results from this study suggest that, even at concentrations far below official guideline levels, radon may lead to a 2.5-fold rise in the risk of lung cancer. Furthermore, the synergy found between smoking and radon may prove useful when it comes to drafting public health recommendations. *Am J Epidemiol* 2002;156: 548–55.

case-control studies; lung neoplasms; radon

Abbreviation: CI, confidence interval.

Radon is a ubiquitous gas and an indoor air pollutant in homes (1). When inhaled, radon 222 can have a carcinogenic effect on lung tissue, because of the emission of alpha particles upon decay (2–12). Although experimental animal studies (3–6) and investigations of underground miners (13–16) have yielded evidence of radon's potential carcinogenic effect (2, 4), any extrapolation of these results to the general population must be regarded as somewhat premature (1, 17, 18). In many cases, such extrapolations may either over- (19, 20) or underestimate the risk (21).

To date, epidemiologic studies of the general population have failed to provide clear evidence of any link between radon and lung cancer (1, 18). Whereas some studies are affected by serious methodological flaws (ecologic attribution of radon exposure (22, 23), failure to adjust for smoking (24, 25), or insufficient sample size for detection of signifi-

cant risks (26–28)), others conducted with greater methodological rigor have yielded inconsistent results, either failing to show any effect whatsoever (29–31) or reporting an effect, but only at high or intermediate doses (32–34) or for certain specific histologic types (35–37). There are studies pointing to a certain upward trend in risk, one of which was, however, not significant (30), and a few studies have reported a significant effect at relatively low doses, yet this was limited to women (38, 39) or to specific sections of the study area (40).

This study thus sought to determine the risk of lung cancer associated with exposure to residential radon, focusing in particular on the effect of low doses. These relations were studied in a district of Galicia (northwest Spain; figure 1) that had previously been classified as a high-risk radon emission area (41), because of the porous, granite nature of the

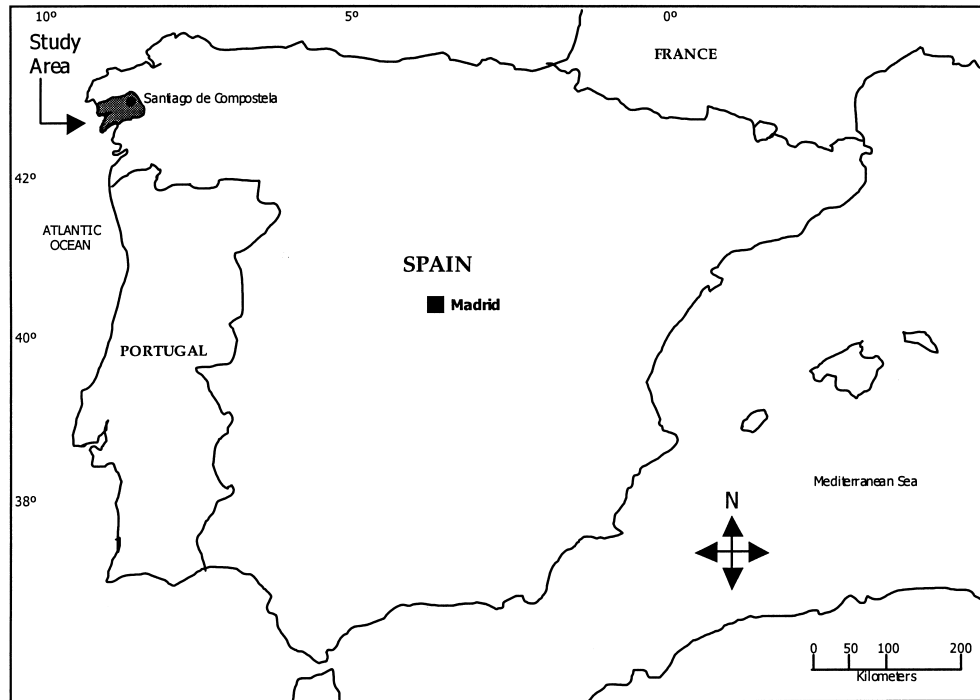


FIGURE 1. Map showing the location of the study on radon and lung cancer, Spain, 1992–1994.

local subsoil. Moreover, granite is the construction material from which most homes in the area are made.

MATERIALS AND METHODS

Design, subjects, and settings

A population-based case-control study was designed to be conducted in the Santiago de Compostela Public Health District (northwest Spain). This district covers a surface area of approximately 5,000 km² (1,900 square miles), has a population of nearly 500,000 inhabitants, and includes rural, urban, and coastal zones.

For study purposes, cases were defined as 257 subjects with anatomicopathologically confirmed incident diagnosis of primary lung cancer in the period 1992–1994 (*International Classification of Diseases*, Ninth Revision). A total of 500 subjects were initially selected as controls, using the 1991 census. To this end, the study area was first divided into five subareas corresponding to *comarcas* (administrative groupings roughly equivalent to a county). Thereafter, proportional stratified random sampling was carried out, based on distribution by sex among cases and the population weighting of each subarea. A minimum age limit of 35 years was imposed on cases and controls alike.

The following exclusion criterion was established for both cases and controls: less than 5 years' uninterrupted residence in the current home and/or residence of any length in any dwelling that had undergone major structural alterations. Cases without histologic confirmation and/or undergoing occupational or therapeutic radiation were also excluded.

Similarly, all persons who were suffering from respiratory tract diseases or who had a clinical history of any type of neoplasia, past or present, were excluded. The final number of subjects that met eligibility criteria included 232 cases and 391 controls.

Data collection, variables, and statistical analysis

All cases and controls or, in the event of intervening death, their closest surviving cohabitants were interviewed individually by two interviewers trained for the purpose. A questionnaire was used to obtain information on all variables of interest pertaining to the study population and their dwellings. The questionnaires had been tested previously with a group of persons who, though not included in the study, had similar characteristics, and all questions that had proved to be poorly drafted or ambiguous were duly amended or eliminated. Radon exposure was measured using alpha-track detectors supplied by Radiation Safety Services, Inc., Morton Grove, Illinois (a US Environmental Protection Agency-approved laboratory) and installed and positioned under standard conditions, namely, in the room in which study subjects spent the most time when at home (generally the bedroom) away from doors and windows and never less than 65 cm from the floor. All detectors were in place in the subjects' homes for a minimum period of 90 days.

Associations between independent variables and outcome (case or control) were modeled using multiple logistic regression. In addition to age and sex, the following were included in the model as possible confounding variables:

TABLE 1. Breakdown of cases and controls by variables of major relevance, Spain, 1992–1994

	Cases	Controls
No. of males (%)	151 (92.6)	219 (90.9)
Age (years) (mean (SD*))	65.7 (10.5)	57.7 (12.5)
No. of subjects with a family history of cancer (%)	28 (18.4)	20 (8.5)
Tobacco consumption		
No. of smokers (%)	145 (91.8)	129 (54.7)
Mean (SD)†	24.2 (16.9)	7.1 (9.9)
Median (pct* 25, 75)†	21.9 (14.6, 35.3)	7.1 (0.0, 10.9)
Radon (Bq/m ³)		
Arithmetic mean (SD)	141.4 (231.9)	114.0 (135.3)
Geometric mean (GSD*)	75.4 (2.4)	66.4 (3.0)
Median (pct 25, 75)	66.6 (40.7, 154.5)	51.8 (29.6, 118.4)
Time of occupancy in dwelling (years)		
5–9 (%)	13 (8.0)	35 (14.5)
10–19 (%)	35 (21.5)	62 (25.7)
≥20 (%)	114 (69.9)	142 (58.9)
Presence of monitoring device (days) (mean (SD))	155.3 (31.1)	150.9 (55.3)

* SD, standard deviation; pct, percentile; GSD, geometric standard deviation.

† Thousands of packs smoked over a lifetime.

smoking habit (defined as the number of packs smoked over a lifetime, categorized in quartiles); family history of lung cancer; habitat (coastal or inland); type of profession; age and type of dwelling (construction material); and daily number of hours spent at home. Two models were used, one with radon measures in tertiles and the other in quartiles. Only those variables showing an association with lung cancer or, alternatively, a confounding effect on the relation between radon and lung cancer were included in the final model. Results were expressed as odds ratios and 95 percent confidence intervals. Population attributable risks were calculated using the exposed proportion of cases and adjusted odds ratios (42, 43) for domestic radon, assuming the latter to be dichotomous. The 95 percent confidence intervals of the population attributable risks were computed using the substitution method (44).

The possible interaction between smoking and exposure to radon was assessed using both a multiplicative model and an additive model. To avoid having a very low number of subjects in the interaction strata, we categorized the variables of exposure to radon and smoking as dichotomous variables, namely, tobacco in smokers and nonsmokers and radon levels of 0–36.9 Bq/m³ and of 37.0 Bq/m³ or more. An alternative model was also used to group nonsmokers plus light smokers (with a cutpoint of 7,300 packs, equivalent to one pack/day for 20 years) because there were only two nonsmoker cases exposed to less than 37 Bq/m³. The confi-

dence intervals of the multiplicative model were calculated using the method of Figueiras et al. (45). In the additive model, the proportion of risk attributable to interaction was computed (46), with the method proposed by Hosmer and Lemeshow (47) being used to estimate the confidence levels of these indices.

RESULTS

A total of 163 cases (151 men and 12 women) and 241 controls (219 men and 22 women), 70.2 percent and 61.6 percent of those eligible, respectively, took part in the study (table 1). In all, 32.3 percent of the controls selected refused to participate versus 27.1 percent of the cases and, after three attempts, 5.3 percent of the controls were not located versus 2.5 percent of the cases. Home detectors were in place for a mean of 152 (standard deviation, 46.7) days and a median of 150 days. For various reasons, residential radon readings could not be obtained for eight homes.

Figure 2 shows the distribution of the study population by radon measurement. The arithmetic mean radon concentration was 129.5 (standard deviation, 136.9) Bq/m³ and the geometric mean, 69.3 (geometric standard deviation, 2.8) Bq/m³. In 22.2 percent of the homes studied, radon concentrations were 148 Bq/m³ or more (4 pCi/liter), with 26.4 percent of the cases and 19.4 percent of the controls exposed to this level of risk.

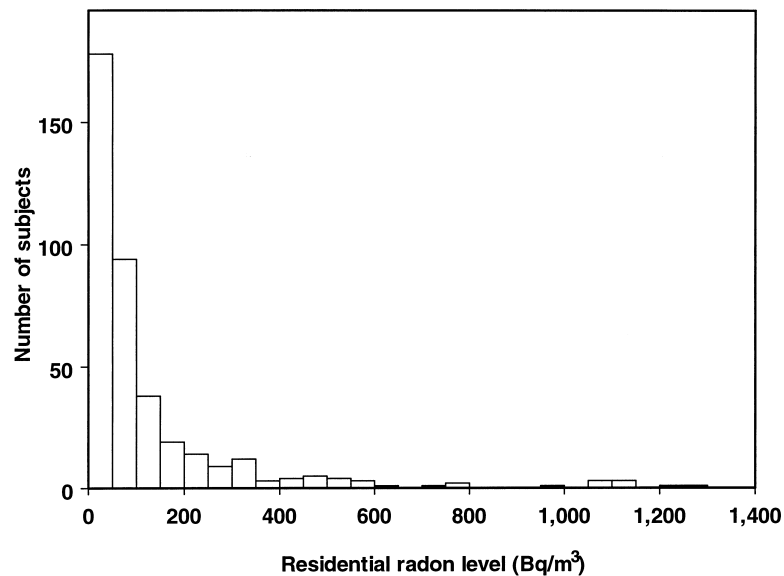


FIGURE 2. Distribution of the study population by residential radon level, Spain, 1992–1994.

Table 2 shows the results of the relation between indoor radon concentration and lung cancer, adjusted for age, sex, smoking habit (by quartiles of lifetime consumption), family history, and type of habitat. For 37 Bq/m³ or more, that is, second, third, and fourth quartiles, a significant, greater than twofold rise in the risk of lung cancer was in evidence. When a radon distribution in tertiles (cutpoints: 40.8 and 88.8 Bq/m³) was used, the risks for each were, respectively, 1.65 (95 percent confidence interval (CI): 0.82, 3.17) and 1.89 (95 percent CI: 0.97, 3.69).

Assuming a prevalence of exposure similar to that observed in controls (68.0 percent), the population attributable risks of lung cancer with exposure to radon were 54.1 percent (95 percent CI: 20.3, 75.0) when the breakpoint was 37.0 Bq/m³ (table 3) and 9.0 percent (95 percent CI: -4.3, 26.8) when it was 148 Bq/m³.

The results with respect to the interaction between smoking and radon exposure are shown in table 3. Smokers exposed to radon levels of 37 Bq/m³ or more were observed to have a risk (odds ratio = 46.45, 95 percent CI: 8.46,

254.85) of suffering lung cancer 46 times higher than that of nonsmokers exposed to radon concentrations below 37 Bq/m³; when the reference category of nonsmokers plus light smokers was used, the risk was 30.10 (95 percent CI: 8.98, 100.90) for smokers exposed to 37 Bq/m³ or more. With application of the multiplicative model, the risk faced by smokers versus nonsmokers exposed to radon (risk ratio = 46.4) exceeded the product of the independent effects ($1.81 \times 20.1 = 36.4 < 46.4$), although this model did not prove statistically significant. With application of the additive model, over half (57 percent) of the cases among smokers exposed to radon concentrations of 37 Bq/m³ or more were observed to be attributable to the synergic effect of radon and tobacco use (95 percent CI: 26.4, 83.2).

DISCUSSION

The results of this study suggest that residential radon constitutes a risk factor for lung cancer. Although reported elsewhere (32, 33), this is the first study to find that, at low

TABLE 2. Effect of radon concentration on the risk of lung cancer, Spain, 1992–1994

Radon concentration*		No. of subjects		Crude analysis		Adjusted analysis†	
Bq/m ³	pCi/liter	Cases	Controls	OR‡	95% CI‡	OR	95% CI
0–36.9	0.0–0.9	28	73	1.00	1.15, 3.75	1.00	1.21, 6.18
37.0–55.1	1.0–1.4	43	54	2.08	1.05, 3.34	2.73	1.12, 5.48
55.2–147.9	1.5–3.9	46	64	1.87	1.30, 4.36	2.48	1.29, 6.79
≥148.0	≥4.0	42	46	2.38	1.30, 4.36	2.96	1.29, 6.79

* Categorized in quartiles for all subjects and expressed in Bq/m³ and pCi/liter.

† Adjusted for age, sex, family history, and lifetime tobacco consumption (measured in packs and categorized in quartiles).

‡ OR, odds ratio; CI, confidence interval.

TABLE 3. Interaction between exposure to radon and lifetime tobacco consumption, Spain, 1992–1994

Lifetime tobacco consumption	Radon concentration		No. of subjects		Adjusted* analysis	
	Bq/m ³	pCi/liter	Cases	Controls	OR†	95% CI†
Nonsmokers	0–36.9	0.0–0.9	2	28	1.00	
	≥37.0	≥1.0	11	76	1.81	0.33, 10.09
Smokers	0–36.9	0.0–0.9	24	43	20.16	3.43, 118.55
	≥37.0	≥1.0	118	85	46.45	8.46, 254.85

* Adjusted for age, sex, and family history.

† OR, odds ratio; CI, confidence interval.

doses, namely, more than 37 Bq/m³ (1 pCi/liter), radon constitutes a risk factor for the general population. Moreover, unlike other studies in which a weak association was found (32, 33, 35), this study points to an over twofold rise in the risk of lung cancer at and above these low exposure levels. Indeed, these data indicate that a synergic effect between radon and smoking, which favors the appearance of lung cancer, is already in evidence at 37 Bq/m³ or more.

The role played by exposure to residential radon and its progeny in the appearance of lung cancer has been the subject of controversy for the last 20 years. Since the results of the first studies on miners were published and subsequently extrapolated to the general population (17, 18), researchers have shown unflagging interest in the subject. Laboratory data on animals (3–6, 48) and on normal or hybrid human cells (10, 49) confirm the carcinogenic potential of alpha radiation released during the radioactive transformation of radon progeny, polonium in particular. Yet such laboratory-based evidence is not mirrored when domestic radon is studied, because the results of epidemiologic studies have proved inconsistent, as is evident from the meta-analysis of Lubin and Boice (18). Similarly inconsistent results have been yielded by ecologic studies: Although most fail to report any relation (50), some claim to have found an association with such factors as latitude (51) or soil type (52). In recent years, all of these inconsistencies have given rise to an interesting debate as to methodology (53–57).

However, the most recent case-control studies (such as those conducted in Sweden (32), Moscow (38), Germany (40), England (58), Missouri (59), and Iowa (60)) appear to be lending ever greater support to the association between radon and lung cancer, although this study is the first to report this relation at low doses (>37 Bq/m³) for all subjects and throughout the study area.

According to the data, the population impact of exposure to the US Environmental Protection Agency's action level—measured as attributable risk (9.0 percent)—does not differ much from that reported by other authors, who place it at somewhere between 5 percent and 10 percent (61–63). However, because these results indicate that a clear effect is already in evidence at low exposures, this gives a population attributable risk that is from 5 to 6 times higher in this study versus others (61, 62).

With respect to the interaction between smoking and exposure to radon, most studies that have set out to analyze this

relation have reported finding it, though they differ on the precise characteristics. In our case, we found a clear and significant additive interaction, which accounted for nearly 60 percent of all cases of lung cancer affecting residential smokers in households registering 37 Bq/m³ or more. These results were seen to coincide with those reported by other studies (14, 39, 63–69), despite the fact that some of the latter used different terminology to describe the interaction (14, 39, 62, 64, 69) or failed to assess its statistical significance. The multiplicative model is less frequent in the literature (68, 70). On the other hand, the synergies reported in other studies tend to correspond to radon levels higher than those reported here and/or to more intense smoking levels (35). Then again, many studies present no analysis of this interaction (31, 34). The importance of this finding lies in the fact that it allows for the drafting and issue of preventive lung cancer guidelines based on the dual status of subjects who are smokers—even occasional or passive smokers (71)—and, simultaneously, residents in dwellings with high radon levels (72).

The explanation for this finding on radon may, in part, lie in the geographic area studied. Northwest Spain can be considered a risk area, because nearly 25 percent of all homes in the study registered radon concentrations equal to or exceeding 148 Bq/m³. Equivalent percentages were as low as 6.7 percent in the first Missouri study (30), rising to 13 percent in the Spanish study (41) and 20 percent in the Chinese study (35). Indeed, this percentage is surpassed only by those obtained in a study undertaken in the British Isles (58) and in another in Finland (36). The high concentrations of residential radon observed here are probably due to the granite nature of the subsoil in the study area, an area that has a geologic profile closely akin to that of north Portugal and southwest England. Nevertheless, this characteristic alone cannot explain the appearance of risk at concentrations much lower than those defined as the “action level” in the United States for many years (61). It is arguable that these results might, in part, be due to inter- (73) or intraannual (74) variations in radon concentrations. However, against this are the facts that installation of detectors was carried out on a parallel basis among cases and controls and that, although adjustment was made for this variable in the statistical analysis, it failed to alter the results to any substantial degree.

The different results yielded by our study may also be attributable to aspects of methodology. The cutoff points

established in our study correspond to quartiles of radon exposure for all subjects as a whole. This dose-response relation is consistent, because the relation remains in evidence when tertiles are used. In previous studies, the variable "radon" was categorized using narrow exposure intervals (30), something that can lead to low statistical power (26, 27, 37). Other studies make use of wider reference categories, which may dilute the possible risks (18, 31, 32). The results reported show that the magnitude of risk posed to the upper three quartiles is over twice that posed to the first. This dose-response relation would seem to indicate that there is no threshold dose or that, if there is, it must lie below the guideline values recommended as safe under both American (2, 75) and European (76) regulations.

Different dosimetry equipment and measurements tend to make comparisons between studies difficult. Not only are there differences in the types of detector used (58–60), but there are also differences in the duration and timing of measurements. The authors relied on long-term alpha-track measurement devices, which have become widely used in the last 10 years. For study purposes, we opted for a monitoring period of 5 months under standard conditions. Although this is a shorter monitoring period than that favored by some studies (29–33, 35), it is nevertheless in line with the mean period reported by others (58). We feel that a 5-month measurement is likely to be long enough to avoid the effects of occasional variations that could possibly interfere with measurements based on a shorter monitoring period.

With regard to timing, the ideal is obviously to have measurement of exposure coinciding with the period in which the effect takes place. However, in this study, as in others covering the same topic (18, 29–33, 35, 36, 38, 58), risk exposure was estimated on the basis of concentrations detected subsequent to the date of diagnosis. Although this may well constitute the main limitation on research, it can nevertheless be assumed that, when subjects have not changed residences and/or the dwelling has undergone no substantial structural alteration, the exposure will not have varied to any substantial degree since the radon exercised its carcinogenic effect. In the case in point, two thirds of all subjects had lived for over 20 years in the dwellings where the readings were taken, there being no significant differences in this respect between cases and controls. Another limitation of the study could be the differential proportion between cases and controls in the use of next of kin. The use of next of kin is very widespread in epidemiology (31). Moreover, for cases suffering from a disease such as lung cancer, a disease with such a short survival time, this approach is fundamental if a sufficient number of subjects are to be enrolled. We cannot see that this situation would give rise to bias in the estimate of the principal variable, namely, radon, because this is a determination made by analytic means rather than on the basis of an interview.

The results yielded by our study suggest that, even at concentrations far below official guideline levels (148 and 200 Bq/m³) (75, 76), radon may lead to a twofold or greater increase in the risk of lung cancer. These results could well prove of great interest when it comes to implementing preventive measures in the home and/or drawing up new

indoor air-quality standards. Furthermore, although a reduction in smoking (with all its ensuing complexity) might achieve better results in the prevention of lung cancer than would a reduction in radon alone (77), our data suggest a synergy between tobacco use and radon that may well prove extremely useful when issuing public health recommendations (along the lines seen in other countries in recent years) (72, 78, 79), targeting the study area and, in particular, households with substantial radon levels and heavy smokers (80).

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