Research Article

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Residential Radon Exposure, Histologic Types, and Lung Cancer Risk. A Case–Control Study in Galicia, Spain

Juan Miguel Barros-Dios[1,2,3], Alberto Ruano-Ravina[1,3], Mónica Pérez-Ríos[1,3], Margarita Castro-Bernárdez[4], Jose Abal-Arca[5], and Marta Tojo-Castro[6]

Abstract

Background: Lung cancer is an important public health problem, and tobacco is the main risk factor followed by residential radon exposure. Recommended exposure levels have been progressively lowered. Galicia, the study area, has high residential radon concentrations. We aim (i) to assess the risk of lung cancer linked to airborne residential radon exposure, (ii) to ascertain whether tobacco modifies radon risk, and (iii) to know whether there is a lung cancer histologic type more susceptible to radon.

Methods: A hospital-based case–control design was conducted in two Spanish hospitals. Consecutive cases with histologic diagnosis of lung cancer and controls undergoing trivial surgery not tobacco-related were included. Residential radon was measured using standard procedures. Results were obtained using logistic regression.

Results: Three hundred and forty-nine cases and 513 controls were included. Radon exposure posed a risk even with a low exposure, with those exposed to 50 to 100 Bq/m^3 having an OR of 1.87 [95% confidence interval (CI), 1.21–2.88] and of 2.21 (95% CI, 1.33–3.69) for those exposed to 148 Bq/m^3 or more. Tobacco increased appreciably the risk posed by radon, with an OR of 73 (95% CI, 19.88–268.14) for heavy smokers exposed to more than 147 Bq/m^3. Less frequent histologic types (including large cell carcinomas), followed by small cell lung cancer, had the highest risk associated with radon exposure.

Conclusions: The presence of airborne radon even at low concentrations poses a risk of developing lung cancer, with tobacco habit increasing considerably this risk.

Impact: Public health initiatives should address the higher risk of lung cancer for smokers exposed to radon.

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Introduction

Lung cancer is a major health problem in developed countries. It is the leading cancer in incidence and mortality in males and the second cause of mortality in females (1). Spain has an intermediate position in the European Union (EU) about lung cancer incidence in males. The adjusted standardized rate (ASR) for the EU is 73.2 cases per 100.000 and 77.8 for Spain. For females, Spain is one of the countries with the lowest incidence in the EU, with an ASR of 10.7 whereas the EU ASR is 22.2 (2). Survival has hardly improved in the last 30 years, with a 12% 5-year survival rate (3). Tobacco is the main risk factor of lung cancer; 79% of all cases in men and 47% in women are attributed to tobacco consumption (4).

Radon is the second cause of lung cancer after smoking and the first in never-smokers (5). Health authorities in many countries have developed radon exposure maps to predict residential radon exposure to enable citizens to implement protective measures where necessary. The Environmental Protection Agency (EPA) action level (6) is 148 Bq/m^3 and the World Health Organization (WHO) has recently lowered the recommended radon exposure to levels below 100 Bq/m^3 (7). WHO policies stem mainly from the results of 2 pooled case–control studies conducted in Europe and North America which showed a 16% and 11% increase in risk of lung cancer for each 100 Bq/m^3, respectively (8, 9). Galicia, the study area, has high radon emissions due to the granitic nature of the earth crust. Around 19% to 21% of all dwellings are above the EPA action level (10, 11), which is an extremely high percentage compared with other areas where radon studies have been conducted.

Many case–control studies have analyzed the association between airborne radon exposure and lung cancer,

Authors' Affiliations: [1]Department of Preventive Medicine and Public Health, University of Santiago de Compostela; [2]Service of Preventive Medicine, University Hospital of Santiago de Compostela, Galician Health Service, Santiago de Compostela, Galicia; [3]CIBER de Epidemiología y Salud Pública, CIBERESP, Madrid; [4]Service of Preventive Medicine, Hospital of Ourense, Ourense; [5]Neumology Service, Hospital of Ourense, Ourense; and [6]Spanish National Genotyping Center, Institute of Evolutionary Biology (CSIC-UPF), Universitat Pompeu Fabra, Barcelona, Spain

Corresponding Author: Alberto Ruano-Ravina, Department of Preventive Medicine and Public Health, School of Medicine, San Francisco street, s/n., Santiago de Compostela 15782, Spain. Phone: 34-881 812237; Fax: 34-881-872282; E-mail: alberto.ruano@usc.es

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but few have analyzed in detail the effect of radon exposure for different categories of smoking. This is important as tobacco is the main risk factor for lung cancer and most cases occur in smokers who are somewhat exposed to radon. Furthermore, scarce investigations have studied the effect of radon exposure below action levels and also the possible interaction with tobacco consumption at these concentrations. There is some controversy about the existence of a radon threshold. While some authors state that low levels pose no threat or are even protective (12), others have found a high risk at low radon levels (10) stating that there is no safe radon concentration (7).

Few studies have analyzed the effect of radon exposure on lung cancer histologic types. Some results have indicated that radon could pose a higher risk for small cell carcinoma (SCC) than for other histologic types (9), although evidence is conflicting (13). The study of radon influence on histology could provide further insight on the biologic effects of alpha radiation, which have not been completely elucidated.

The objectives of this study are, through a hospital-based case–control study, (i) to analyze low residential airborne radon exposure on the risk of lung cancer, (ii) to assess whether radon modifies the effect of different categories of tobacco consumption, and (iii) to study whether radon poses a higher risk for a specific histologic type.

Material and Methods

Design, subjects, and settings

A hospital-based case–control study was conducted in Galicia, northwest Spain between 2004 and 2008. The investigation took place in 2 centers: Santiago de Compostela University (Santiago de Compostela, Galicia, Spain) Teaching Hospital and Ourense Hospital Complex (Ourense, Spain). These hospitals cover a population of approximately 700,000 and have full capacity to diagnose and treat lung cancer.

Cases and controls younger than 30 years of age and those individuals with previous cancers were excluded. Cases had an anatomopathologically confirmed lung cancer and were recruited through consecutive sampling from lung cancer cases diagnosed throughout the study period. The histologic type of the participants was ascertained from the pathologic anatomy records.

Controls were recruited from those individuals attending both hospitals for nontobacco-related trivial surgery. Controls were sex frequency–matched with cases and both had to have lived at least 5 years in the last dwelling to be included. Approximately 90% of the controls were scheduled to have orthopedic surgery, cataract surgery, or surgery for inguinal hernias. All participants were asked to give written consent for participation in the research. The study protocol was approved by the Galician Clinical Research Ethics Committee (REF 2004/108).

Data collection and radon measurement

All subjects were interviewed at the hospital using a questionnaire which inquired about various lifestyle aspects with special emphasis on smoking habits and radon exposure. Interviews were conducted by trained staff immediately after diagnosis for cases. With respect to smoking, subjects were asked about the number of daily cigarettes, duration of the smoking habit, years since quitting (in the case of ex-smokers), and type of tobacco consumed.

On the basis of information obtained from studies on miners (14, 15), we assumed that the induction period for lung cancer was from the previous 30 years ending 5 years before the diagnosis for cases and the recruitment date for controls, respectively. Radon measurements were conducted with alpha-track detectors (CR-39, Radosys Inc.) at the Galician Radon Laboratory at the Santiago de Compostela University Teaching Hospital. The detectors were placed and picked up from participants' homes by a specialist radon technician. Detectors were placed away from doors, windows, and electric devices, between 60 and 180 cm from the floor. Radon was measured for a period of 3 to 6 months. Seasonal adjustments were conducted when the detectors were revealed and quality controls on the measurements were conducted periodically. The Galician Radon Laboratory measurement processes have passed a quality control test by the Nuclear Safety Council of Spain with excellent results (16).

Statistical analysis

A bivariate descriptive analysis was conducted to determine the distribution of the study variables according to the case or control status. This was followed by a multivariate logistic regression where the dependent variable was the case or control status and the independent variable was radon exposure broken down into 4 categories (<50, 50–100, 101–147, and >147 Bq/m^3). As adjustment variables, we included age (continuous), gender, and tobacco consumption divided into 4 categories: never-smokers and smokers divided into 3 categories (tertiles) according to lifetime tobacco consumption. The cutoff points for these tertiles were 1–33, 34–66 and >66 pack-years. We present crude and adjusted results for this and other models using multivariate logistic regression.

We formally tested the possible additive or multiplicative interaction among tobacco consumption and residential radon exposure. To do this, we created a variable with 4 categories classifying individuals as exposed or nonexposed to radon (using 50 Bq/m^3 as the cutoff point) and smokers were classified as never- or ever-smokers. The confidence intervals of the multiplicative model were calculated using the method proposed by Figueiras and colleagues (17). For the additive model, we calculated the synergy index and the confidence intervals using the method proposed by Hosmer and Lemeshow (18). We further analyzed the combined effect of radon exposure and tobacco consumption through creating a variable with 16 categories (4 categories of radon exposure and 4

of tobacco consumption). The reference category was never-smokers exposed to less than 50 Bq/m^3. This analysis was adjusted by age and sex.

A further analysis was done analyzing the effect of radon exposure on the risk of lung cancer histologic types. To facilitate the comparison of the results, a different logistic regression was used for each histologic type with the same controls as the reference group (19). Four regressions were conducted corresponding each to squamous cell type, adenocarcinoma, small cell lung cancer, and other histologic types, all adjusted by age, gender, and tobacco consumption. Radon exposure and tobacco consumption were included in 4 categories as aforementioned.

Results are expressed as ORs with 95% confidence intervals (CI). Analyses were conducted with SPSS version 17.

Results

The participation rates were high, 90.4% of contacted cases and 76% of contacted controls fulfilling the inclusion criteria took part in the study. In all, 990 individuals were included, 442 cases and 548 controls. A total of 862 individuals had radon measurements (349 cases and 513 controls, 79% and 93.6% of those included, respectively). A complete tobacco history was not available for all 862 participants; there were 70 individuals with missing characteristics on some tobacco variables that did not allow calculating lifetime tobacco consumption (i.e., daily consumption, age at starting and/or age at cessation, which impedes calculating smoking duration and therefore lifetime tobacco consumption). Because calculating radon risks without adjusting for tobacco consumption is not useful due to tobacco's importance on the onset of lung cancer, we decided to exclude these individuals from all the analyses.

Cases and controls had a similar age and sex distribution, reflecting the frequency sampling used for these variables. A sample description broken down by case–control status can be observed in Table 1. Cases and controls had similar education level; however, tobacco consumption was much higher among cases than among controls. Regarding radon exposure, there were more cases than controls exposed to the highest radon exposure categories. About 18.6% and 20.1% of cases were exposed to 101–147 and >147 Bq/m^3 compared with 14% and 15% of controls. The predominant histologic type among cases was squamous cell carcinoma (46.4% of all cases) followed by adenocarcinoma (26.4%).

We found that lung cancer risk increased with radon exposure. The risk was statistically significant departing from 50 Bq/m^3 with an OR of 1.87 (95% CI, 1.21–2.88). Those exposed to residential radon levels higher than 147 Bq/m^3 had an OR of 2.21 (95% CI, 1.33–3.69). Lung cancer risk hardly changed after adjusting the results with tobacco consumption (Table 2).

Regarding radon and tobacco interaction, we have found an additive interaction when we classified individuals as exposed (≥50 Bq/m^3) or nonexposed to residential radon and smokers in never- or ever-smokers. The synergy index for this interaction was 2.19 (95% CI, 1.38–3.49; $P < 0.001$). We did not find a multiplicative interaction ($P = 0.19$). When we further analyzed the interaction

Table 1. Sample description broken down by case–control status (N = 862)

Variable	Cases, *n* (%)	Controls, *n* (%)
Age		
≤50 y	23 (6.6)	52 (10.1)
51–70 y	177 (50.7)	315 (61.4)
>70 y	149 (42.7)	146 (28.5)
Gender		
Female	47 (13.5)	63 (12.3)
Male	302 (86.5)	450 (87.7)
Education (highest education attained)		
No formal studies	34 (9.8)	34 (6.6)
Primary school	275 (79.5)	389 (75.8)
High school	24 (6.9)	69 (13.5)
University degree	13 (3.8)	21 (4.1)
Tobacco consumption[a,b]		
Never-smokers	47 (15.3)	220 (45.5)
Light smokers (first tertile, 1–33 pack-years)	42 (13.6)	140 (28.9)
Moderate smokers (second tertile, 34–66 pack-years)	95 (30.8)	82 (16.9)
Heavy smokers (third tertile, >66 pack-years)	124 (40.3)	42 (8.7)
Residential radon exposure, Bq/m^3		
<50	84 (24.1)	193 (37.6)
50–100	130 (37.2)	171 (33.3)
101–147	65 (18.6)	72 (14.0)
>147	70 (20.1)	77 (15.0)
Presence of cellar in the measured dwelling		
Yes	105 (34.5)	173 (36.2)
No	199 (65.5)	305 (63.8)
Years living in the measured dwelling		
Median	30	30
Percentiles (25–75)	17.5–45	16–42
Histologic types		
Squamous cells carcinoma	162 (46.4)	
Adenocarcinoma	92 (26.4)	
SCC	54 (15.5)	
Large cell carcinoma	20 (5.7)	
Other types	21 (6.0)	

[a]Smokers classified by lifetime tobacco consumption.
[b]N = 792, including only those individuals with complete tobacco information.

Table 2. Risk of lung cancer broken down by radon exposure

Variable	Cases, *n* (%)	Controls, *n* (%)	OR[a] (95% CI)	OR[b] (95% CI)
Residential radon exposure, Bq/m^3				
<50	77 (25.0)	184 (38.0)	1 (—)	1 (—)
50–100	112 (36.4)	157 (32.4)	1.80 (1.25–2.60)	1.87 (1.21–2.88)
101–147	56 (18.2)	69 (14.3)	1.90 (1.20–2.97)	2.25 (1.32–3.84)
>147	63 (20.5)	74 (15.3)	2.17 (1.39–3.37)	2.21 (1.33–3.69)
Tobacco consumption				
Never-smokers	47 (15.3)	220 (45.5)		1 (—)
Lifetime tobacco consumption (first tertile)	42 (13.6)	140 (28.9)		3.57 (1.96–6.49)
Lifetime tobacco consumption (second tertile)	95 (30.8)	82 (16.9)		16.96 (9.21–31.21)
Lifetime tobacco consumption (third tertile)	124 (40.3)	42 (8.7)		37.27 (19.81–70.21)

[a]Adjusted by age and sex.

[b]Adjusted by age, sex, and tobacco consumption (never-smokers and smokers divided into tertiles according to lifetime tobacco consumption).

among residential radon exposure and tobacco consumption through the construction of 16 categories of exposure (4 for tobacco consumption and 4 for radon exposure), we observed an increase in the risk of lung cancer when radon exposure increases for similar tobacco consumption (Table 3). For example, heavy smokers exposed to radon levels below 50 Bq/m^3 have a risk of 28.36 (95% CI, 10.91–73.73) that increases to 73.0 (95% CI, 19.88–268.14) when they are exposed to more than 147 Bq/m^3. For the remaining tobacco categories, there is an increase in the risk of lung cancer from the lowest exposure to radon concentration (<50 Bq/m^3) to the highest exposure (>147 Bq/m^3). Nevertheless, the risk of lung cancer fluctuates for the middle categories of radon exposure for each tobacco tertile. The exception is for never-smokers, where the increase in radon exposure seems to have no effect on lung cancer risk, although median radon concentration for never-smoking cases was 103 Bq/m^3 and 70 Bq/m^3 for controls.

Regarding lung cancer histologic types, radon increases the risk of all histologic types and appears to pose a higher risk for small cell lung cancer and other histologic types than for squamous cell carcinoma and adenocarcinoma (Table 4). For these 2 histologic types, the risk is marginally significant, but for SCCs and other histologic types, the risk with the highest radon exposure is 2.43 (95% CI, 0.79–7.45) and 5.58 (95% CI, 1.68–18.58), respectively.

Discussion

The results of this study show that airborne residential radon poses a risk for lung cancer far below action levels postulated by health organizations. Individuals exposed to concentrations higher than 50 Bq/m^3 have close to a 2-fold risk of lung cancer compared with those exposed to lower concentrations. Radon exposure also acts as an effect modifier of tobacco consumption. For those with a similar tobacco habit, the increase in radon exposure increases the risk of lung cancer. However, this is not so for never-smokers, for whom radon seems to have no effect. Finally, SCCs and other histologic types (those different from squamous cell and adenocarcinoma but

Table 3. Interaction among tobacco and residential radon exposure and risk of lung cancer

	Tobacco consumption (cases, controls); OR[a] (95% CI)			
Residential radon exposure	**Never-smokers**	**First tertile**	**Second tertile**	**Third tertile**
0–50	12, 82	5, 48	27, 39	33, 15
	1 (—)	1.23 (0.39–3.96)	10.0 (4.14–24.24)	28.36 (10.91–73.73)
51–100	11, 67	19, 53	32, 22	50, 15
	0.89 (0.34–2.32)	4.82 (1.98–11.72)	22.18 (8.84–55.65)	47.0 (18.47–119.61)
101–147	13, 39	7, 17	17, 5	19, 8
	1.39 (0.53–3.62)	5.07 (1.58–16.24)	51.47 (14.71–180.04)	29.78 (9.81–90.42)
>147	11, 32	11, 22	19, 16	22, 4
	1.16 (0.42–3.22)	7.46 (2.62–21.19)	18.47 (6.77–50.42)	73.0 (19.88–268.14)

[a]Adjusted by age and sex.

Table 4. Residential radon exposure and risk of the different histologic types of lung cancer

Variable	Cases, *n* (%)	Controls, *n* (%)	Crude OR[a] (95% CI)	Adjusted OR[b] (95% CI)
Squamous cell lung cancer				
Residential radon exposure, Bq/m^3				
<50	41 (28.1)	184 (38.0)	1 (—)	1 (—)
50–100	57 (39.0)	157 (32.4)	1.78 (1.1–2.83)	2.04 (1.19–3.51)
101–147	23 (15.8)	69 (14.3)	1.66 (0.91–3.02)	1.94 (0.96–3.94)
>147	25 (17.1)	74 (15.3)	1.88 (1.04–3.39)	1.86 (0.95–3.66)
Adenocarcinoma				
Residential radon exposure, Bq/m^3				
<50	21 (24.4)	184 (38.0)	1 (—)	1 (—)
50–100	26 (30.2)	157 (32.4)	1.41 (0.76–2.64)	1.44 (0.75–2.79)
101–147	20 (23.3)	69 (14.3)	2.06 (1.03–4.13)	2.27 (1.08–4.75)
>147	19 (22.1)	74 (15.3)	1.91 (0.95–3.86)	1.78 (0.86–3.73)
Small cell lung cancer				
Residential radon exposure, Bq/m^3				
<50	10 (23.8)	184 (38.0)	1 (—)	1 (—)
51–100	16 (38.1)	157 (32.4)	1.94 (0.85–4.42)	1.85 (0.75–4.59)
101–147	9 (21.4)	69 (14.3)	2.50 (0.96–6.50)	3.01 (1.01–8.97)
>147	7 (16.7)	74 (15.3)	2.08 (0.75–5.77)	2.43 (0.79–7.45)
Other histologic types of lung cancer				
Residential radon exposure, Bq/m^3				
<50	5 (14.7)	184 (38.0)	1 (—)	1 (—)
52–100	13 (38.2)	157 (32.4)	3.03 (1.05–8.75)	3.23 (1.04–10.00)
101–147	4 (11.8)	69 (14.3)	1.90 (0.49–7.40)	1.75 (0.41–7.44)
>147	12 (35.3)	74 (15.3)	5.89 (1.96–17.72)	5.58 (1.68–18.58)

[a]Adjusted by age and sex.
[b]Adjusted by age, sex, and tobacco consumption (never-smokers and smokers divided into tertiles according to lifetime tobacco consumption).

including large cell carcinoma) are the most influenced by radon exposure.

These results are in agreement with a previous study by our group carried out using a smaller sample and in a more limited geographical area (10). The study showed a significant risk of lung cancer for those with exposures to radon ranging between 37 and 55 Bq/m^3 compared with those exposed to lower concentrations (OR, 2.73; 95% CI, 1.12–5.48). Other studies have found risk for radon exposure but not as high as ours at low exposures (20). The 2 radon pooling studies conducted in Europe and North America found a linear relationship between radon and lung cancer risk (8, 9). Different statistical models were tested and the one which better fit the data was a linear model. These studies found an increase in risk of 11% and 16% per each 100 Bq/m^3, respectively. This assumes that there is no safe radon exposure and encouraged WHO to lower the threshold level to 100 Bq/m^3, far below official guidelines in most countries (7). This no-threshold risk is supported by experimental studies where one-hit of an alpha particle to a cell can lead to a permanent change and also to by-stander effects on adjacent cells. Such observations support the existence of a pernicious effect of radon on lung cancer even with very low exposures (14, 21, 22).

The biologic mechanism of alpha radiation cell damage is not well known. Some evidence shows that radon exposure could induce mutations in critical genes involved in regulating cell division such as *p53* (23, 24). Nevertheless, the results of the different studies are conflicting, and only 3 studies have assessed the cell damage caused by residential radon exposure. While some have associated radon exposure with hotspot regions (25), others have not shown any effect (26). A possible mechanism could involve susceptibility genes such as *GSTM1* but only one study has assessed its interaction with radon exposure with a case-only design (27).

Our study has shown an additive interaction between radon exposure and tobacco consumption. This result is very similar to our previous study, where the additive interaction was in evidence even at low radon exposures (10). Heavy smokers exposed to more than 147 Bq/m^3 had a risk 73 times higher than never-smokers exposed to less than 50 Bq/m^3. This risk is nearly 3-fold that of heavy smokers with the least radon exposure. Other studies have found interactions of variable intensity between radon and smoking. The North American pooling showed a similar effect for radon across smokers and never-smokers. The lung cancer risk due to radon did not vary with

the duration of smoking or number of cigarettes smoked per day (9, 19). Other studies, such as the Iowa Radon Lung Cancer study, did not show differences in the effect of residential radon on different smoking categories (28). A synergic effect between radon and tobacco in lung cancer incidence is biologically plausible. Some experimental studies have shown that tobacco and radon could interact, raising the risk of lung cancer (14). This synergistic effect has been observed both in *in vitro* studies and also in research conducted in rats and dogs exposed to radon and environmental tobacco smoke (29). Experimental studies in humans are not possible and the only possible approach is to include individuals with a high radon exposure as is the case of miners. Nevertheless, most studies conducted on miners obtain indirect information about tobacco consumption, making again extrapolations to residentially exposed individuals very complicated. The carcinogenic biologic mechanism for both risk factors is different and therefore the possibility of synergism is highly plausible. Research conducted on radon exposure effect on *p53* gene supports the hypothesis of a different effect from radon than that caused by tobacco, with different mutational characteristics for each risk factor (23). Studies on radon attributing to lung cancer mortality provide indirect evidence of this joint effect between tobacco and radon. Whereas attributable mortality exclusively due to radon exposure is very low, in most lung cancer deaths, smoking is present with more or less intensity (30, 31).

The present study has found no effect of radon exposure in never-smokers. Other studies, such as the North American pooling, have found similar results (9). Sandler and colleagues (32) did not find an effect for nonsmokers in the Connecticut and Utah study and the same occurred for the Iowa study (28). In a recent ecological study on radon and lung cancer in the American Cancer Society Cohort, it was found that the risk from radon exposure was higher for current smokers whereas for never-smokers radon posed no risk. For former smokers, the risk was intermediate though nonsignificant (33). Other studies have reported opposite results. Wilcox and colleagues showed that radon risk was higher for never-smokers than for ever-smokers (34). This was also the case in the European Pooling Study (8). In this study, radon posed a significant risk for lung cancer in never-smokers departing from 100 Bq/m^3 [relative risk (RR), 1.1; 95% CI, 1.0–1.2]. This risk was 1.7 (95% CI, 1.2–2.3) for those exposed to concentrations higher than 800 Bq/m^3 (35). Studies on miners yield contradictory results. Schubauer-Berigan and colleagues observed that the risk of lung cancer was higher for smokers than for never-smokers. For the latter, there was risk of lung cancer only for those exposed to high radon concentrations (36). Other study observed that radon exposure produced a higher excess of relative risk (ERR) in never-smoker miners than in smokers. This ERR was also higher for ex-smokers than for current smokers (37). Nevertheless, we should highlight that in the present study, there were only 47 never-smoking cases, and the maximum number of cases in each radon exposure category was 13. Median radon concentration was 33 Bq/m^3 higher for cases than for controls with these differences increasing slightly as radon concentration increases (data not shown).

The results of the present study show that the highest risk of lung cancer is associated with uncommon histologic types (including large cell carcinomas) followed by SCCs. For other histologic types, the OR is 5.5 (95% CI, 1.6–18.6) for the highest category of radon exposure (>147 Bq/m^3) whereas for small cell lung cancer, it is 2.4 (95% CI, 0.8–7.4). Although the latter OR was not statistically significant (with only 7 cases in this category), the previous one reached statistical significance, with an OR of 3. Other studies have obtained similar results. The American Pooling reported the highest risk for small cell lung cancer followed by other histologic types (9). This study used the same controls when analyzing different histologic types, as did the present study (19). The European Pooling also revealed the highest risk for SCCs (35) whereas other studies found the highest risks for large cell carcinomas (OR, 3.4) followed by SCCs (OR, 3.2; ref. 28). A similar result was in evidence for males and females in the study conducted by Wilcox and colleagues (34) and in a further study the highest risk was observed for other histologic types (32). Nevertheless, other investigations obtained different results, failing to find differences between histologic types (13). Studies conducted in miners (WISMUT Mining Company) have revealed a higher incidence of small cell lung cancer (50% of all lung cancers) than other histologic types. Squamous cell lung cancers also appeared earlier than the others. Radon exposure was similar between squamous cell lung cancers and SCCs but lower for adenocarcinomas. When comparing SCCs with squamous cell lung cancers, it was observed that the risk of both histologic types was similar for cumulative radon exposure but lower for SCCs about duration of exposure (38). It is striking that most studies that assessed the effect of radon on lung cancer histologic types have not discussed the results obtained from a biologic point of view. We suppose that this is due to the lack of experimental studies or biologic evidence explaining the reasons because radon can be more of a risk for some histologic types than for others.

The present study has some advantages. The sample size is enough to calculate the joint effect of radon and tobacco consumption and also the differential effect of radon exposure on lung cancer histologic types. Radon exposure is high, as 15% of participants are exposed to radon levels higher than 148 Bq/m^3—meaning that we have enough individuals in each radon category for calculating risks and to conduct a subgroup analysis without a relatively low uncertainty. A last advantage is that 65.9% of the analyzed subjects have lived for more than 20 years in the measured dwelling. Furthermore, the median time of occupancy of the measured dwelling has been 30 years for both cases and controls. Galician people have low mobility than other European or American populations,

which facilitates the attribution of the radon concentration measured to the risk of lung cancer.

This study also has some limitations. Perhaps, the main one is the possibility of recall bias. Nevertheless, radon exposure is an objective measurement that is not subjected to this bias, and the interviewers were specially trained to address the possibility of recall bias for tobacco habit. Cases were interviewed immediately after diagnosis to facilitate recruitment because many of them had an advanced disease and also for avoiding misperceptions in their tobacco reporting due to a lung cancer diagnosis. Other limitation is the low sample size when studying the effect of radon on histologic lung cancer types. Cases had to be divided into categories losing statistical power for calculating precise effects. The histologic type with the lowest number of cases was other histologic types (including large cell carcinoma) with 41 cases. Although it is not a high number, it is enough to observe the existence of a tendency for radon effect. The participation rate was higher for cases than for controls. However, the difference was only 15% (90% vs. 76%) and we do not think that these differences can affect the results given that both were high and there are no studies which suggest that radon concentration (which is *a priori* unknown) influences participation rates.

The results yielded by our study point out that radon is a risk factor for lung cancer even with exposures considered low by international guidelines, including the WHO report (7). Some estimations indicate that to reduce the overall number of radon attributing to lung cancer deaths in the United States by 50% radon concentrations in all homes could not exceed 74 Bq/m^3 (39). There is also an additive synergic effect between radon and tobacco consumption, as smokers exposed to high radon concentrations pose a very high risk of lung cancer than in smokers exposed to low concentrations. Furthermore, radon appears to have a greater influence on small cell lung cancer and other less frequent histologic types than on adenocarcinoma and squamous cell carcinoma. Therefore, public health initiatives should address the higher risk of lung cancer for smokers exposed to radon, without forgetting that the best way to prevent lung cancer is not to smoke.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J.M. Barros-Dios, A. Ruano-Ravina, M. Pérez-Ríos, M. Castro-Bernárdez, M. Tojo-Castro
Development of methodology: J.M. Barros-Dios, A. Ruano-Ravina
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A. Ruano-Ravina, M. Castro-Bernárdez, J.A. Arca, M. Tojo-Castro
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.M. Barros-Dios, A. Ruano-Ravina, M. Pérez-Ríos
Writing, review, and/or revision of the manuscript: J.M. Barros-Dios, A. Ruano-Ravina, M. Pérez-Ríos, M. Castro-Bernárdez, J.A. Arca, M. Tojo-Castro
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A. Ruano-Ravina
Study supervision: J.M. Barros-Dios, A. Ruano-Ravina, M. Pérez-Ríos, M. Castro-Bernárdez

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Juan Miguel Barros-Dios, Alberto Ruano-Ravina, Mónica Pérez-Ríos, et al.

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