Lung cancer in never-smokers: a case–control study in a radon-prone area (Galicia, Spain)

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ABSTRACT The aim of the study was to assess the effect of residential radon exposure on the risk of lung cancer in never-smokers and to ascertain if environmental tobacco smoke modifies the effect of residential radon.

We designed a multicentre hospital-based case–control study in a radon-prone area (Galicia, Spain). All participants were never-smokers. Cases had an anatomopathologically confirmed primary lung cancer and controls were recruited from individuals undergoing minor, non-oncological surgery. Residential radon was measured using alpha track detectors.

We included 521 individuals, 192 cases and 329 controls, 21% were males. We observed an odds ratio of 2.42 (95% CI 1.45–4.06) for individuals exposed to $\geqslant$200 Bq·m^{-3} compared with those exposed to $<$100 Bq·m^{-3}. Environmental tobacco smoke exposure at home increased lung cancer risk in individuals with radon exposure $>$200 Bq·m^{-3}. Individuals exposed to environmental tobacco smoke and to radon concentrations $>$200 Bq·m^{-3} had higher lung cancer risk than those exposed to lower radon concentrations and exposed to environmental tobacco smoke.

Residential radon increases lung cancer risk in never-smokers. An association between residential radon exposure and environmental tobacco smoke on the risk of lung cancer might exist.

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Introduction

Lung cancer is currently the leading cause of cancer death worldwide. Tobacco consumption is the most important risk factor for lung cancer; however, between 15–25% of all lung cancer cases occur in never-smokers [1]. Recent research suggests that lung cancer in never-smokers could be a different disease than lung cancer in smokers, since different molecular pathways are present in never-smokers' lung cancer [2, 3]. These patients also have higher survival, a different age of onset and have mainly adenocarcinomas [4, 5].

Residential radon exposure is the second risk factor of lung cancer after tobacco consumption and the first risk factor for never-smokers [6]. Residential radon was declared a human carcinogen in 1987 by the World Health Organization (WHO) and in 1988 by the US Environmental Protection Agency (EPA). The US EPA considers an action level of 148 $Bq \cdot m^{-3}$ whereas WHO has recently lowered the action level to 100 $Bq \cdot m^{-3}$[6, 7].

Two pooling studies, which included case–control studies performed in Europe and North America, found a linear relationship between residential radon exposure and lung cancer risk [8, 9]. The European pooling included 884 never-smoker cases and 5418 never-smoker controls. In the latter subgroup, there is an excess of relative risk of 10.6% per 100 $Bq \cdot m^{-3}$ was observed, slightly higher than the risk observed for ex- and current-smokers. In the American pooling study there was no difference between ever- and never-smokers for risk of lung cancer. In both groups the excess of relative risk was 10%. Very few case–control studies [10–12] have been performed that have included never-smokers and the results are conflicting. A recent systematic review [13] suggests a possible relationship between residential radon exposure and lung cancer in never-smokers and it seems that there is a dose–response pattern.

A problem that appears when assessing the relationship between residential radon and lung cancer is the low variability in radon concentrations, which makes it difficult to assess possible dose–response patterns. Galicia, the study area, has been characterised as a radon-prone region by previous studies [14, 15]. Furthermore, Galician population has low mobility compared with other populations, which facilitates the attribution of lung cancer to radon exposure [15].

Environmental tobacco smoke (ETS) is a risk factor for lung cancer. In 1992, it was recognised as a human carcinogen by the US EPA [16]. Only one study has suggested that there is a synergism between residential radon and ETS [12]. This synergism could be explained because radon and tobacco smoke may have a different carcinogenic mechanism, with different mutational patterns for each risk factor [17].

The aim of the present study is to assess the effect of residential radon exposure on the risk of lung cancer in never-smokers and to ascertain if ETS exposure can modify the effect of residential radon.

Material and methods

Design and setting

We designed a multicentre hospital-based case–control study in the Northwest of Spain (Galicia and Asturias). All public hospitals in Galicia (n=7) and the most important hospital in Asturias (Hospital Central de Asturias) took part. 95% of the patients in the study population area had universal healthcare coverage. Lung cancer diagnosis and staging was only performed in the hospitals included in the study. The study area comprised of both urban and rural areas, and ~50% of the population lived in detached houses in the countryside.

Cases and controls were recruited between January 2011 and June 2013. All participants were never-smokers. A never-smoker was defined as: 1) an individual reporting <100 cigarettes in a lifetime or 2) had not smoked for 6 months. To be included, cases had to have an anatomopathologically confirmed lung cancer. Cases and controls had to be aged >30 years with no upper age limit. Individuals with previous cancers were excluded. Cases were identified by pneumologists assigned to the lung cancer rapid-diagnosis pathway at each hospital.

Controls were recruited from ambulatory individuals undergoing minor, non-oncological surgery. The following hospitals provided controls: Santiago de Compostela, Ourense, Vigo and Lugo; the first three hospitals cover geographic areas that have slightly higher residential radon concentrations than the Lugo area. Controls were selected using a frequency sampling on age and sex distribution regarding cases in order to assure comparability between cases and controls on these two variables.

The study protocol was approved by the Galician Committee of Research Ethics (reference 2010/295) and all participants signed written consent for participation.

Data collection and radon measurement

All participants were personally interviewed at hospital by trained researchers using a questionnaire. They were asked about different aspects of their lifestyle, with special emphasis on ETS exposure, leisure time

exposures, diet, and alcohol consumption. Participants provided a biological sample of 3 mL of blood in order to analyse genetic polymorphisms and its relation with lung cancer onset.

We retrieved detailed information on ETS exposure from all participants. We asked them if they had or had not lived with a smoker during the last 20 years. In an affirmative case we asked about the relationship, the number of years of cohabitation, and the number of cigarettes per day smoked by the cohabitant. We collected information of up to four smoking cohabitants. We also collected information for ETS exposure during childhood or at work. Since the most relevant exposure for lung cancer appearance is ETS at home and due to changes regarding smoking at work (enforced by law) in the recent years, we only considered ETS exposure at home in our analysis.

The interviewer gave the participants a radon detector to take home and positioning instructions, which included a picture on how to correctly position the detector in the home. Participants also received a prepaid envelope to send back the detector to the coordinating centre once the measurement period had finished. The detector was of the alpha-track type (CR-39; Radosys Inc., Budapest, Hungary). The detector was placed in the participant's bedroom, at a height between 60 and 180 cm from the floor, away from doors, windows, heating and electrical devices. The minimum period of exposure was 3 months. 1 week after the detector was given to the patient, a researcher phoned the participant. This was undertaken in order to ensure the correct positioning of the device and to answer any doubts or questions the participant may have had. Once the exposure period finished, another phone call was made to inform the participant that he/she should send back the radon detector. Specific instructions for sealing the device, once it was retired from use, were given. The devices were read at the Galician Radon Laboratory (Santiago de Compostela, Spain), which has been certified by the University of Cantabria, with excellent results in intercomparison exercises [18]. We also performed periodical quality controls with blanks and sending detectors to other radon laboratories for intercomparison purposes. Radon measurements were seasonally adjusted in order to consider radon variability throughout the year. We sent to the participants the results of the radon measurements, with specific recommendations depending on the radon concentration observed at each home.

Statistical analysis

We performed a bivariate descriptive analysis to determine the distribution of the study variables according to the case or control status. Following this analysis, we used a multiple logistic regression where the dependent variable was the case or controls status and the independent variable residential radon exposure broken down in four categories ($\leqslant$100, 101–147, 148–199 and $\geqslant$200 Bq·m^{-3}). As adjustment variables, we introduced in the model age (continuous), sex, and ETS exposure defined as having lived with a smoker or not for >20 years. We repeated the same analysis but only including females and also including only individuals who had lived $\geqslant$20 years in the same dwelling.

To assess if ETS exposure at home, defined as the time living with a smoker modified the risk of lung cancer due to residential radon, we created a variable with six categories through syntaxes. This variable combined two categories for residential radon (<200 and $\geqslant$200 Bq·m^{-3}) and three for years living with a smoker (0, 1–35 and $\geqslant$36 years). The results were adjusted by age and sex. All the results are expressed as odds ratios with 95% confidence intervals. The software used for the analysis was IBM SPSS v20 (IBM, Armonk, NY, USA).

Results

521 individuals, 192 cases and 329 controls were included. The participation rate was high, >90% of cases and 75% of controls accepted to took part in the study. 15 cases (7.8% of the total included) were recruited in Asturias. The sex distribution was very similar among cases and controls and also the age distribution. 21% were males and the median age was 70 years for cases and controls. Education levels were similar between both groups and the percentage of individuals who had worked in risk occupations for lung cancer did not differ between cases and controls. More cases than controls lived in rural areas, but there were no statistically significant differences between radon concentrations in each of the habitats, though residential radon was slightly higher in rural areas. Radon exposure was considerably higher among cases compared with controls. 48% of cases had residential radon exposure >200 Bq·m^{-3} compared with 29.4% for the controls. The returning rate of radon detectors was 177 (92.2%) out of 192 for cases and 272 (82.6%) out of 329 for controls. The median number of years living in the measured home was 30 years for cases and 36 years for controls. The percentage of controls living with smokers in adulthood was 45.1% compared with 42.2% in cases ($p=0.051$). Regarding histological types, 77.5% had adenocarcinoma, followed by 10.0% with squamous cell carcinoma. The sample characteristics appear on table 1.

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TABLE 1 Patients in the study characteristics

Variable	Cases	Controls
Patients n	192	329
Age years median (range)/25–75 percentile	70 (34–87)/61–77	70 (43–90)/63.5–79
Sex		
Female	153 (79.7)	259 (78.7)
Male	39 (20.3)	70 (21.3)
Education		
No formal studies	49 (26.1)	51 (15.5)
Primary school	114 (60.6)	246 (74.7)
High school	13 (6.9)	19 (5.8)
University degree	12 (6.4)	13 (4.0)
Have worked in risk occupations for lung cancer#		
No	163 (87.2)	281 (87.3)
Yes	24 (12.8)	41 (12.7)
Participant's habitat		
Urban	77 (40.5)	74 (22.6)
Rural	113 (59.5)	254 (77.4)
Residential radon exposure Bq·m^{-3}		
⩽100	36 (20.3)	73 (26.9)
101–147	24 (13.6)	61 (22.4)
148–199	32 (18.1)	58 (21.3)
⩾200	85 (48.0)	80 (29.4)
Years living in the measured dwelling median (25–75 percentiles)	30 (17–44)	36 (20–52)
Exposure to ETS at home in the last 20 years		
Yes	81 (42.2)	148 (45.1)
No	111 (57.8)	180 (54.9)
Histological types		
Adenocarcinoma	148 (77.5)	
Squamous cell carcinoma	19 (10.0)	
Small cell carcinoma	12 (6.3)	
Large cell carcinoma	6 (3.1)	
Other histological types	6 (3.1)	

Data are presented as n (%) unless otherwise stated. ETS: environmental tobacco smoke. #: following the classification proposed by AHRENS AND MERLETTI [19].

Regarding the effect of residential radon on lung cancer risk in never-smokers, we observed an OR of 2.42 (95% CI 1.45–4.06) for individuals exposed to concentrations >200 Bq·m^{-3}, taking those individuals exposed to <100 Bq·m^{-3} as a reference. The other exposure categories did not show a significant effect. When we restricted the analysis to only females, we observed an OR 2.84 (95% CI 1.58–5.09) for those exposed >200 Bq·m^{-3}. Finally, for individuals who had lived for ⩾20 years in the same dwelling, we found 1.83 OR (95% CI 1.01–3.30) when patients were exposed to ⩾200 Bq·m^{-3} compared with those exposed to <100 Bq·m^{-3}. The effect of radon exposure on lung cancer risk can be observed in table 2.

The effect modification, due to exposure to ETS, on the relationship between residential radon and lung cancer is shown in table 3. The risk of lung cancer does not increase with the number of years living with a smoker for individuals exposed to residential radon <200 Bq·m^{-3}. Nevertheless, for individuals exposed to >200 Bq·m^{-3} the risk of lung cancer is higher for all categories of ETS exposure when compared with their counterparts exposed to radon levels <200 Bq·m^{-3}. Individuals exposed to >200 Bq·m^{-3} and who have not lived with a smoker show a risk of 1.99 (95% CI 1.16–3.41) and this risk changes to 2.75 (95% CI 1.44–5.25) for those who have lived 1–35 years with a smoker. The last category has a nonsignificant OR of 0.63, although there were only seven cases and 20 controls in it.

Discussion

The results of the present study show that residential radon increases the risk of lung cancer in never-smokers when they are exposed to indoor levels >200 Bq·m^{-3}. The risk is more than two-fold when compared with those participants exposed to levels <100 Bq·m^{-3}. The risk is similar for females and for individuals having

TABLE 2 Residential radon exposure and risk for lung cancer

	Radon exposure Bq·m^{-3}			
	⩽100	101–147	148–199	⩾200
Patients				
Cases	36 (20.3)	24 (13.5)	32 (32.8)	85 (48)
Controls	73 (26.8)	61 (22.4)	58 (21.3)	80 (29.4)
OR (95% CI)[#]	1[§]	0.84 (0.45–1.56)	1.14 (0.63–2.06)	2.33 (1.40–3.89)
OR (95% CI)[¶]	1[§]	0.80 (0.43–1.50)	1.16 (0.64–2.11)	2.42 (1.45–4.06)
Females				
Cases	29 (20.7%)	20 (14.3%)	24 (17.1)	67 (47.8)
Controls	60 (28.3%)	46 (21.7%)	51 (24.01)	55 (25.9)
OR (95% CI)[+]	1[§]	0.87 (0.43–1.75)	1.00 (0.52–1.95)	2.84 (1.58–5.09)
Patients at same dwelling ⩾20 years				
Cases	30 (24.6)	15 (12.3)	22 (18.0)	55 (45.1)
Controls	57 (28.8)	37 (18.7)	37 (18.7)	67 (33.8)
OR (95% CI)[¶]	1[§]	0.76 (0.36–1.61)	1.18 (0.59–2.36)	1.83 (1.01–3.30)

Data are presented as n (%) unless otherwise stated. [#]: adjusted for sex and age; [¶]: adjusted for sex, age and environmental tobacco-smoke exposure at home; [+]: adjusted for age and environmental tobacco-smoke exposure at home; [§]: no confidence interval as reference category.

lived ⩾20 years in the same dwelling. Our study is the first to suggest a possible association between residential radon exposure and ETS on the risk of lung cancer.

The present study provides important insights into the health effects of radon exposure in never-smokers, since very few case–control studies have been performed in never-smokers. We observed that the risk becomes significant when levels of radon are >200 Bq·m^{-3}; however, the action level as recommended by US EPA is 148 Bq·m^{-3} and WHO recently recommended the action level as 100 Bq·m^{-3} [6, 7]. The US EPA and WHO recommendations are based on studies that mainly involved ever-smokers [8, 9]. There is an interaction between radon and smoking on the risk of lung cancer, additive or submultiplicative [8, 15, 20], therefore, the residential radon concentrations necessary to promote lung cancer in ever-smokers should be lower than in never-smokers. The present results confirm this hypothesis; where a significant risk of lung cancer appears only at high concentrations of residential radon (>200 Bq·m^{-3}). This holds true when analysing joint exposure to ETS and indoor radon. In the current study it was decided to use 100, 148 and 200 Bq·m^{-3} as the cut-off points for radon exposure. 100 Bq·m^{-3} had to be used as the first category because few individuals were exposed to radon concentrations <50 Bq·m^{-3} (n=26). However, this first radon level cut-off point is higher than those used in other studies [8, 11, 12, 21–23]. The second cut-off point corresponded to the US EPA action level (148 Bq·m^{-3}), and the final cut-off point (200 Bq·m^{-3}) is the recommended indoor radon concentration for new houses in the European Union [24].

Available studies on radon and lung cancer in never-smokers show quite similar results. However, most of them were not designed to assess the risk of lung cancer in never-smokers and only present the results as a subanalysis of the main research [8, 9, 21, 23, 25, 26,]. Studies that exclusively involved never-smokers or had a high sample size of never-smokers in the overall sample, observed a linear increase in excess of the relative risk (ERR) with exposure to residential radon of 0.106 (95% CI -0.09–0.42) per 100 Bq·m^{-3} in the European pooling study [8] and an ERR of 0.28 (95% CI -0.05–1.05) in the study by LAGARDE *et al.* [12]. The two most important studies performed in never-smokers are the European pooling study [8] and the study by LAGARDE *et al.* [12]. Both studies have shown a dose–response effect for radon and lung cancer in never-smokers. The European pooling study shows a statistical significant effect from 100 Bq·m^{-3} (OR 1.23, 95% CI 1.02–1.48) and the risk increases with radon exposure. The study by LAGARDE *et al.* [12] shows a significant effect at 140 Bq·m^{-3} (OR 1.4, 95% CI 1.0–2.1). These results show that the risk for lung cancer might be evident at <200 Bq·m^{-3} for never-smokers. A recent systematic review published by our group [13], concluded that it seems to be a dose–response relationship between residential radon and lung cancer in never-smokers. Nevertheless, the results obtained by the different case–control studies mainly depend on the study setting, with those investigations performed in radon-prone areas tending to obtain significant risks and those in areas with low-dose residential radon showing no effect [11].

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TABLE 3 Environmental tobacco-smoke exposure, residential radon and risk of lung cancer

Radon[#] Bq·m^{-3}	Living with smokers in the same dwelling[¶] years											
	0				1–35				⩾36			
	Total	Cases	Controls	OR (95% CI)	Total	Cases	Controls	OR (95% CI)	Total	Cases	Controls	OR (95% CI)
<200	174	64	110	1[+]	75	21	54	0.57 (0.31–1.06)	36	8	28	0.44 (0.19–1.03)
⩾200	84	44	40	1.99 (1.16–3.41)	53	33	20	2.75 (1.44–5.25)	27	7	20	0.63 (0.25–1.56)

Data are presented as n unless otherwise stated. [#]: residential exposure [¶]: odds ratio adjusted for sex and age; [+]: no confidence interval as reference category.

The slightly higher risk of lung cancer observed when only females were analysed could be due to several explanations: hormonal factors, higher exposure to passive smoking than males [27], or in fact that Galician females spend more time at home than males, since most of the included females were housewives.

An interesting result is the effect modification observed with ETS exposure and residential radon. For individuals exposed to >200 Bq·m^{-3} the risk of lung cancer increases with the number of years living with a smoker, with the exception of the last category that was composed of individuals who had lived >35 years with a smoker. For this category there were only 27 individuals, seven cases and 20 controls and, therefore, this particular result cannot be considered conclusive. ETS and radon are human lung carcinogens [28, 29] and it is biologically plausible an association between both risk factors. Since there is an interaction between radon and active smoking, an interaction between radon and ETS is highly possible. Nevertheless, lung cancer risk entailed by ETS exposure is much lower than that posed by active smoking and, therefore, we would need higher radon concentrations and prolonged periods of ETS exposure to find out if such an association exists. In our case, we divided ETS exposure at home into three categories, taking into account that for active smoking it is the duration of smoking that is more important than the number of cigarettes smoked per day for lung cancer risk [30]. The possibility of a joint effect could also be supported due to the different carcinogenic mechanisms of ETS substances [31, 32] and radon exposure, which is largely unknown [17]. It is important to highlight that ETS exposure is very difficult to measure. A latency period for lung cancer induction has not been defined and there is no consensus about the best way to measure (and integrate) the effects of ETS exposure than can come from different sources [33]. Nevertheless, ETS exposure at home is the most relevant exposure for lung cancer.

The present study has been performed in a radon-prone area, which is an important advantage because it allows the assessment of dose–response effect of residential radon. In fact, the high levels of radon in Galicia places the population in a natural experiment [34]. Previous studies [14, 15] have observed that ~10–12% of Galician dwellings have residential radon levels >200 Bq·m^{-3}. In the present study 29.4% of the controls had residential radon >200 Bq·m^{-3}. The difference is probably due to previous studies not including areas of Southern Galicia that have naturally high levels of radon, which we included in the present study. There are two more remarkable advantages. The first advantage was the high rate of radon devices returning from cases and controls, > 90% for cases and 80% for controls. This was due to the thorough follow-up with the participants, mainly through phone calls. To our knowledge, these figures are the highest reported in the literature. The second advantage is the high number of years that the participants have lived at the same home. The median number of years in the measured dwelling was 30 years and 36 years for cases and controls, respectively, and a low percentage lived <20 years. These results are similar to other studies [15, 35], facilitating an easier attribution of lung cancer to radon exposure in comparison with other settings. Finally, the multicentre nature of our study increases its external validity and has allowed the achievement of a relatively high sample size, considering that lung cancer in never-smokers is a rather infrequent disease.

Our study also has some limitations. We have not been able to separately analyse the effect of residential radon on males, since the frequency of never-smoking males is low, with only 20% of all cases being male. Other investigation in the same area observed similar results [15], with 23.4% of males in a large series of never-smoking lung cancer cases. The percentage is also similar (20.7%) in a study performed in Taiwan, with >1500 lung cancer cases [16]. Regarding ETS there is no standardised measurement for this exposure [33] and we have chosen as a proxy for this exposure the years living with a smoker in the same home without considering the number of daily cigarettes per day for each inhabitant. Nevertheless, the

measurement of ETS is extremely complex, because we should take into account the number of cigarettes smoked in the presence of the participant, the number of days (including or not the days during the weekend) and so on. Recall bias might be present, with cases trying to make a greater effort in remembering past exposures to ETS compared with controls. This information bias could be greater for individuals who have lived for a longer period with a smoker. Our trained interviewers tried to avoid this bias performing standardised interviews. There is a low possibility of a selection bias for the included lung cancer cases and controls. Practically all the population living in the studied area has universal healthcare coverage and, to our knowledge, lung cancer diagnosis is not undertaken outside of the participating hospitals. Since the radon device was given at the time of diagnoses, there is a very low probability of selection bias for cases. Controls were selected at four participating hospitals. Three of these hospitals are placed in areas known to have slightly higher residential radon concentrations and this fact could bias the results towards the null hypothesis (no effect for radon). This has not been the case. When we have analysed the results excluding lung cancer cases from hospitals, with *a priori*, lower radon concentrations in their catchment area (Asturias, La Coruña, Lugo and Ferrol), the results varied very little (data not shown). These hospitals contributed with 56 cases, accounting for 29% of all cases.

To conclude, residential radon is a risk factor for lung cancer in never-smokers. The risk is apparent for levels >200 Bq·m^{-3} and is practically the same when we restrict the analysis to females or to individuals who have lived for a minimum of 20 years in the same dwelling. There seems to be a joint effect of residential radon with ETS exposure, with individuals with both exposures having a higher risk of lung cancer. These results support preventive and awareness activities to also be directed to never-smokers, with the objective to reduce their exposure to residential radon. Public health authorities should consider including in their messages the higher risk that is posed by residential radon when ETS is present.

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