Science of the Total Environment 610–611 (2018) 1125–1132

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

# Residential radon and cancer mortality in Galicia, Spain

Gonzalo López-Abente [a,b,*], Olivier Núñez [a,b], Pablo Fernández-Navarro [a,b], Juan M. Barros-Dios [b,c,d], Iván Martín-Méndez [e], Alejandro Bel-Lan [e], Juan Locutura [e], Luis Quindós [f], Carlos Sainz [f], Alberto Ruano-Ravina [b,c,d]

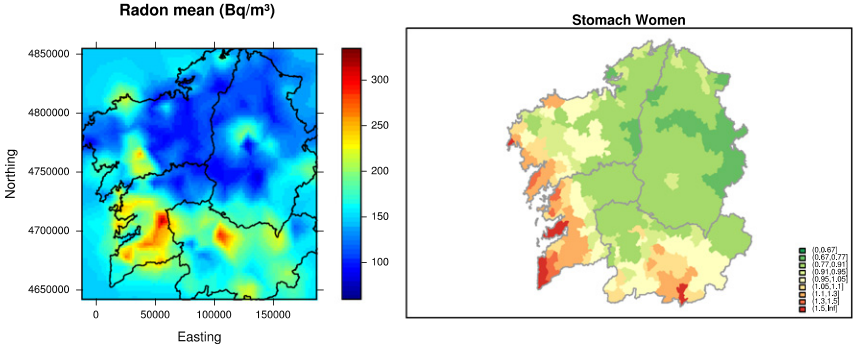
[a] Cancer and Environmental Epidemiology Unit, National Epidemiology Center, Carlos III, Institute of Health, Avda. Monforte de Lemos 5, 28029 Madrid, Spain
[b] Consortium for Biomedical Research in Epidemiology and Public Health (CIBER en Epidemiología y Salud Pública - CIBERESP), Spain
[c] Department of Preventive Medicine and Public Health, University of Santiago de Compostela, School of Medicine, San Francisco Street, 15782 Santiago de Compostela, Galicia, Spain
[d] Preventive Medicine Unit, Santiago de Compostela Clinic University Hospital, Santiago de Compostela, Galicia, Spain
[e] Department of Geochemistry and Mineral Resources, Spanish Geological and Mining Institute (Instituto Geológico y Minero de España/IGME), Ríos Rosas, 23, 28003 Madrid, Spain
[f] RADON Group, Faculty of Medicine, University of Cantabria, c/Cardenal Herrera Oria s/n, 39011 Santander, Cantabria, Spain

## HIGHLIGHTS

- Chronic exposure to indoor radon could be associated with an increase in mortality from lung, stomach and brain cancer.
- Ingestion of water containing dissolved radon would entail exposure of the stomach and other organs of the digestive system.
- The mixed regression models applied allow misaligned data analysis involving a fusion of lattice and geostatistical data.

## GRAPHICAL ABSTRACT

Spatial distribution of radon levels (left) and stomach cancer mortality in women in Galicia (right). Radon levels on the estimation grid are based on the SPDE-INLA model. Municipal distribution of stomach cancer mortality in women, based on BYM modeling, depicts the posterior mean relative risk (RR) for every town across a ten-year period 1999–2008.




## ARTICLE INFO

*Article history:*
Received 14 July 2017
Received in revised form 14 August 2017
Accepted 14 August 2017
Available online 30 August 2017

Editor: D. Barcelo

*Keywords:*
Cancer mortality
Spatial data analysis
Geochemistry
Soil composition
Indoor radon
Residential radon

## ABSTRACT

Residential radon exposure is a serious public health concern, and as such appears in the recommendations of European Code Against Cancer. The objective of this study was to assess the association between residential radon levels and mortality due to different types of cancer, using misaligned data analysis techniques. Mortality data (observed cases) for each of the 313 Galician municipalities were drawn from the records of the National Statistics Institute for the study period (1999–2008). Expected cases were computed using Galician mortality rates for 14 types of malignant tumors as reference, with a total of 56,385 deaths due to the tumors analyzed. The effect estimates of indoor radon (3371 sampling points) were adjusted for sociodemographic variables, altitude, and arsenic topsoil levels (1069 sampling points), using spatial/geostatistical models fitted with stochastic partial differential equations and integrated nested Laplace approximations. These models are capable of processing misaligned data. The results showed a statistical association between indoor radon and lung, stomach and brain cancer in women in Galicia. Apart from lung cancer (relative risk (RR) = 1.09), in which a twofold increase in radon exposure led to a 9% rise in mortality, the association was particularly relevant in stomach (RR = 1.17) and brain cancer (RR = 1.28). Further analytical epidemiologic studies are needed to confirm these results, and

* Corresponding author at: Área de Epidemiología Ambiental y Cáncer, Centro Nacional de Epidemiología, Instituto de Salud Carlos III, Avda. Monforte de Lemos 5, 28029 Madrid, Spain.
*E-mail address:* glabente@isciii.es (G. López-Abente).

http://dx.doi.org/10.1016/j.scitotenv.2017.08.144

Medical geology
Misaligned data

an assessment should be made of the advisability of implementing interventions targeting such exposure in higher-risk areas.



## 1. Introduction

Radon is a gas that can seep into dwelling interiors fundamentally from the soil, though it can also come from water and construction materials. In its radioactive decay, its progeny is inhaled or ingested, leading to the exposure of lung tissue and other organs. Evidence of its carcinogenicity comes from epidemiologic studies on underground miners (uranium and other ores), who worked in areas with high radon levels. The radon exposure levels found in homes are not comparable to those experienced by such miners. Exposure to radon and its consequences are a serious public health concern, and have been included in the recommendations of the European Code Against Cancer (Schüz et al., 2015). Based on the results of general population studies, the 2009 WHO report proposed that exposure levels be lowered to 100 $Bq/m^3$ (Zeeb and Shannoun, 2009).

The possible etiologic relationship between radon and tumor sites other than lung is controversial. Reanalysis of pooled miner data has yielded differing results: in addition to excess deaths from lung cancer, the 28 tumor sites analyzed also displayed significant excess mortality for stomach cancer (O/E 1.33), primary liver cancer (O/E 1.73), and leukemias (O/E 1.93). When cumulative exposure was studied, however, no associations were found (Darby et al., 2005) As a result, Darby et al., concluded that high airborne radon concentrations did not cause a material risk of mortality from cancers, other than lung cancer in miners.

Although the results of ecologic studies were rejected for a number of reasons in "The Health Effects of Exposure to Indoor Radon" report issued by the USA National Research Council Committee on Biological Effects of Ionizing Radiations (BEIR VI) (NRCC-BEIR, 1999), subsequently new ecologic studies were undertaken using a more refined methodology, and some indicated the existence of an association between indoor radon and other cancers. One of these studies used aggregate radon measures from US counties and sought to link these to multiple tumor sites (Turner et al., 2012a; Turner et al., 2012b). It is well established that radon is a cause of lung cancer, yet there is still uncertainty about the dose absorbed by organs other than the lung, arising from exposure to radon progeny (Marsh et al., 2012; Miles and Cliff, 1992; USNRC, 1999), since contradictory results have been published.

The principal source of radon-progeny exposure in homes is emanation from topsoil and rock below ground. In a few special situations, well water or building materials can contribute substantially but they make relatively small contributions to the overall dose (NCRP, 1984). Furthermore, arsenic (As) content in topsoil may have a confounding effect, due to its association with lung cancer and tumors of the digestive tract, and its geologic coexistence with uranium and radium (Nuñez et al., 2016).

The study reported here sought to use data on indoor-radon levels, based on more than 3000 sampling points, and on As content in topsoil, based on a grid of 1600 points, to ascertain their influence on the distribution of cancer mortality in 313 Galician towns. In the literature, this is known as point areal spatial misalignment (Finley et al., 2014), though there are authors who prefer the term, "change of support problem" (Gotway and Young, 2002). In addition to As topsoil content, our analysis took into account sociodemographic variables and municipal altitude, by fitting spatial/geostatistical models suited to the analysis of misaligned data.

The aim of this study was to assess the association between residential radon levels and mortality due to different types of cancer in a radon-prone area such as Galicia (NW Spain).

## 2. Methods

### 2.1. Study setting

Galicia is a region situated in northwestern Spain, bordered to the south by Portugal, to the north and west by the Atlantic Ocean, and to the east by mainland Spain. Half the total population of 2,700,000 lives in the countryside, mainly in single-family detached homes. Public health coverage encompasses 97% of all inhabitants.

### 2.2. Mortality data

A detailed description of the mortality data and soil samples collected can be found in a previously published study (Nuñez et al., 2016). Briefly, mortality data (observed cases) for each of Galicia's 313 towns were drawn from the records of the National Statistics Institute for the study period (1999–2008). Expected cases were computed using Galician mortality rates for 14 types of malignant tumors as reference (Table 1), with a total of 56,385 deaths due to the tumors analyzed.

### 2.3. Radon data. Selection of measuring points. Radon maps in Galicia

The Galician Radon Map (GRM) project is a cross-sectional study conducted by the Galician Radon Laboratory and launched in 1991 at the University Cantabria and in 2001 at the University of Santiago de Compostela. Random sampling based on the 1991 census was performed to select the dwellings to be included in the GRM. The sample was stratified by district and weighted by the population to ensure that districts with a larger population had proportionally more measurements. All subjects over the age of 18 who consented to participate were included in the final study. For completion of the GRM, control measurements from two previous case-control studies on residential radon and lung cancer were also used. A total of 3371 indoor radon measurements were included (Barros-Dios et al., 2012; Torres-Durán et al., 2014b, p.).

Alpha-track type radon detectors CR39 (Radosys Inc., Budapest, Hungary) were installed and, in the majority of cases, positioned in the main bedroom or living room, for a period of 3 to 6 months. The

**Table 1**
Number of deaths due to the different tumors studied: Galicia, 1999–2008.

| Cancer site | ICD-9[a] | ICD-10[b] | Deaths men | Deaths women | Total |
|---|---|---|---|---|---|
| Lung | C33–C34 | 162 | 11,526 | 1809 | 13,335 |
| Buccal cavity and pharynx | C00–C14 | 140–149 | 1492 | 308 | 1800 |
| Oesophagus | C15 | 150 | 1467 | 234 | 1701 |
| Stomach | C16 | 151 | 3286 | 2351 | 5637 |
| Pancreas | C25 | 157 | 2068 | 1763 | 3831 |
| Colorectal | C18–C21 | 153–154, 159.0 | 5742 | 4387 | 10,129 |
| Breast | C50 | 174 | | 4001 | 4001 |
| Prostate | C61 | 185 | 5176 | | 5176 |
| Bladder | C67 | 188 | 2446 | 595 | 3041 |
| Kidney | C64–C66, C68 | 189 | 854 | 418 | 1272 |
| Brain | C71 | 191 | 1008 | 809 | 1817 |
| Thyroid | C73 | 193 | 100 | 195 | 295 |
| Non-Hodgkin's lymphomas (NHL) | C82–C85, C96 | 200, 202 | 1183 | 1062 | 2245 |
| Leukemias | C91–C95 | 204–208 | 1135 | 970 | 2105 |
| Total | | | 37,483 | 18,902 | 56,385 |

[a] ICD-9: International Classification of Diseases, 9th Revision.
[b] ICD-10: International Classification of Diseases, 10th Revision.

detectors were placed well away from doors, windows and electric devices, at a height of 60 to 180 cm off the floor. At the end of the measurement period, the detector strips were revealed under standard conditions in the Galician Radon Laboratory, located at the Santiago de Compostela University Clinical Teaching Hospital. The laboratory's measurement processes underwent quality-control testing by the Nuclear Safety Council of Spain and the accredited ENAC laboratory of the University of Cantabria and were pronounced excellent (Vargas and Ortega, 2007; Vargas and Ortega, 2006; Gutierrez-Villanueva et al., 2013). All radon measurements were adjusted, taking seasonal variations into account.

### 2.4. Arsenic in topsoil

Across the period June 2008 through November 2010, a total of 21,187 residual soil samples (13,505 from the surface horizon and 7682 from the deeper horizon) were collected at a total of 13,505 sampling points (13,317 in mainland Spain, and 188 on the Canary and Balearic islands). For analysis purposes, we used the 1069 samples from Galicia. Unlike topsoil, residual soil is found in the geologic substratum and is therefore not transported. The residual soil samples were analyzed by instrumental inductively coupled plasma mass spectrometry (ICP-MS). The element included in this analysis was As. A detailed description of the sample-collection and chemical-analysis techniques used can be found in the Geochemical Atlas of Spain (Locutura et al., 2012). All laboratory determinations were performed at Activation Laboratories Ltd. (Actlabs, Ontario).

### 2.5. Statistical analysis of spatially misaligned data

Whereas cancer mortality data are aggregated at a town area level, data on residential radon and As topsoil concentrations are measured and recorded at sampling locations across the country. To take this distinction into account, we adopted an approach whereby spatial variations in radon and arsenic concentrations (sampling locations) and in relative risk (RR) of cancer mortality (town locations) were jointly modeled and estimated (spatially misaligned data).

Let $\text{expos}_i$ denote the radon concentrations at each town centroid location $s_i$, and assume for the moment that these values are known. Assume that the observed number of cases $O_i$ in the $i$th area is Poisson distributed with a mean of $E_i\lambda_i$, where $E_i$ is the expected number of cases in that area and the relative risk $\lambda_i$ follows a log-linear model, such that:

$$\log(\lambda_i) = \alpha + \beta\,\text{expos}_i + u_i + v_i \tag{1}$$

where $\alpha$ is an intercept, $\beta$ is the coefficient for the exposure covariate $\text{expos}_i$, $v_i$ are unstructured normal residuals, and $u_i$ are spatially structured effects which follow an intrinsic conditional autoregressive model, namely, the Besag, York and Mollié model (BYM) (Besag et al., 1991). Inference for the primary parameter of interest, $\beta$, is made in a Bayesian framework, and prior distributions are specified for all parameters.

In point of fact, the exposure covariate $\text{expos}_i$ is not directly observed. Instead, we observe the concentrations of radon $r_j$ at sampling locations $s_j$. For these observations, we assume the log-linear model

$$\log(r_j) = \text{Normal}(x_j, \sigma_x^2) \tag{2}$$

where $x_j$ is the realisation of a Matérn Gaussian field at location $s_j$, and $\sigma_x^2$ is a measurement error variance.

It therefore follows that, in the previous model, $\text{expos}_i$ is a latent variable equal to $x_i$ and its relationship with the RR of mortality can be assessed through joint estimation of models (1) and (2). This approach takes into account the heterogeneity of the measurement error in the radon concentration at the centroids, inasmuch as some areas may contain very few sampling points or be characterized by great variability of the radon concentrations lying within them. Consequently, areas that furnish more accurate information about their respective radon concentrations will play a larger role in the inference about the overall exposure effect, $\beta$.

To control for the potentially confounding effect of As topsoil concentrations on this inference, this variable should be included in the model. However, As concentrations were not observed at the town centroids, thus again posing a misalignment problem. As with radon, a log-linear model such as Eq. (2) was therefore used to model the variations of the observed arsenic concentrations.

The Gaussian fields associated with the radon and arsenic concentrations were approximated using the stochastic partial differential equation (SPDE) method (Lindgren et al., 2011; Lindgren and Rue, 2015), as implemented in Integrated Nested Laplace Approximation (R-INLA) (Rue et al., 2009; Rue and Martino, 2010). Both random fields are discretized on the same triangulated mesh of Galicia. The choice of the mesh resolution (number of vertices) is a compromise between the accuracy of this approximation and computational costs. To solve this trade-off, we used an information criterion based on the greatest length of the triangle edge allowed, and tried to reduce the computational load, with the selected value of this length being 3 km. The extension of the mesh with a lower resolution around the Galicia was constructed to control for boundary effects.

In addition to model (1), another ecological regression (Eq. (3)) was considered to account for potential sociodemographic and environmental confounding factors:

$$\log(\lambda_i) = \alpha + \beta\text{radon}_i + \gamma\text{arsenic}_i + \sum_j \delta_j \text{Soc}_{ij} + \theta\text{altitude}_i + u_i + v_i, \tag{3}$$

where the socio-demographic indicators ($\text{Soc}_{ij}$) were obtained from the 1991 census and considered for their availability at the city level and potential explanatory ability vis-à-vis certain geographic mortality patterns (López-Abente et al., 2006). These indicators were: population size (categorized into three levels, i.e., 0–2000 [rural zone], 2000–10,000 [semi-urban zone] and greater than 10,000 inhabitants [urban zone]); percentages of illiteracy, farmers, and unemployment; average number of persons per household; and mean income. The centroid altitude of each town was also included in the models (Kropat et al., 2014). The exposure variable (radon) was transformed by means of its $\log_2$ for the purposes of normalizing it, as required by the model, and facilitating its interpretation. RR was interpreted as the increase in mortality for a twofold increase in exposure.

Maps were plotted showing the spatial distribution of mortality due to selected tumors in men and women across a 10-year period (Galicia 1999–2008). The maps depict the posterior mean RR for every town (mortality versus the average for Galicia) obtained from BYM modeling without explanatory covariates.

**Table 2**
Radon distribution in Bq/m$^3$. and As topsoil levels (mg kg$^{-1}$): Galicia and mainland Spain.

| | N[a] | Min | P(25) | P(50) | Mean | P(75) | Max |
|---|---|---|---|---|---|---|---|
| *Mainland Spain* | | | | | | | |
| Radon[b] | 10,899 | 10.0 | 30.0 | 56.0 | 100.6 | 109.0 | 15,400.0 |
| Radon (averaged)[b] | 5600[c] | 10.0 | 32.0 | 58.1 | 92.4 | 107.6 | 3233.0 |
| Arsenic | 13,317 | 0.1 | 5.3 | 9.0 | 15.1 | 15.3 | 2510.0 |
| *Galicia* | | | | | | | |
| Radon | 3371 | 6.0 | 50.0 | 104.0 | 153.9 | 192.0 | 2756.0 |
| Arsenic | 1069 | 0.1 | 7.1 | 13.1 | 28.5 | 30.1 | 862.0 |

[a] Number of sampling points.
[b] Quindos et al. (2008) and Sainz Fernández et al. (2017).
[c] Number of cells 10 × 10 km.

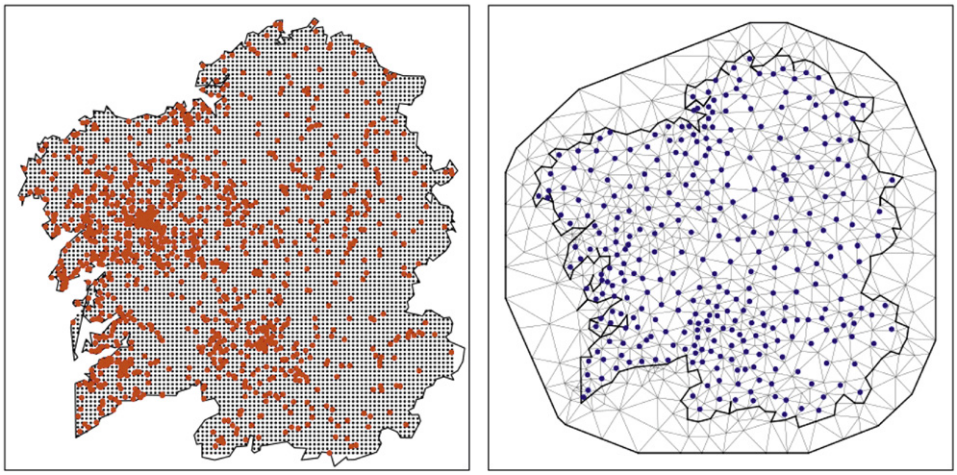


**Fig. 1.** Home sampling points (3371) on an estimation grid (10,201) (left) and triangulation of Galicia (right): blue points denote municipal centroids (313).

## 3. Results

Table 1 shows the number of cases by cancer site. Over the ten-year study period, there were 56,385 cases distributed among the fourteen tumor sites targeted, with the most frequent being lung, colorectal and prostate cancer in men, and colorectal, breast and stomach cancer in women. Indoor radon levels and As topsoil concentrations are shown in Table 2. In Galicia, the interquartile range for radon levels was 53 to 184 Bq/m$^3$, while that for arsenic concentrations was 7 to 30 mg kg$^{-1}$. The median radon level in Galicia was 104 Bq/m$^3$ versus 56 Bq/m$^3$ for Spain as a whole (Quindos et al., 2008).

Fig. 1 shows the distribution of the radon measurement points on the estimation grid and mesh used in the models.

Fig. 2 shows the level plot of posterior mean radon obtained by the SPDE model on the grid and municipalities in Galicia, taking sampling

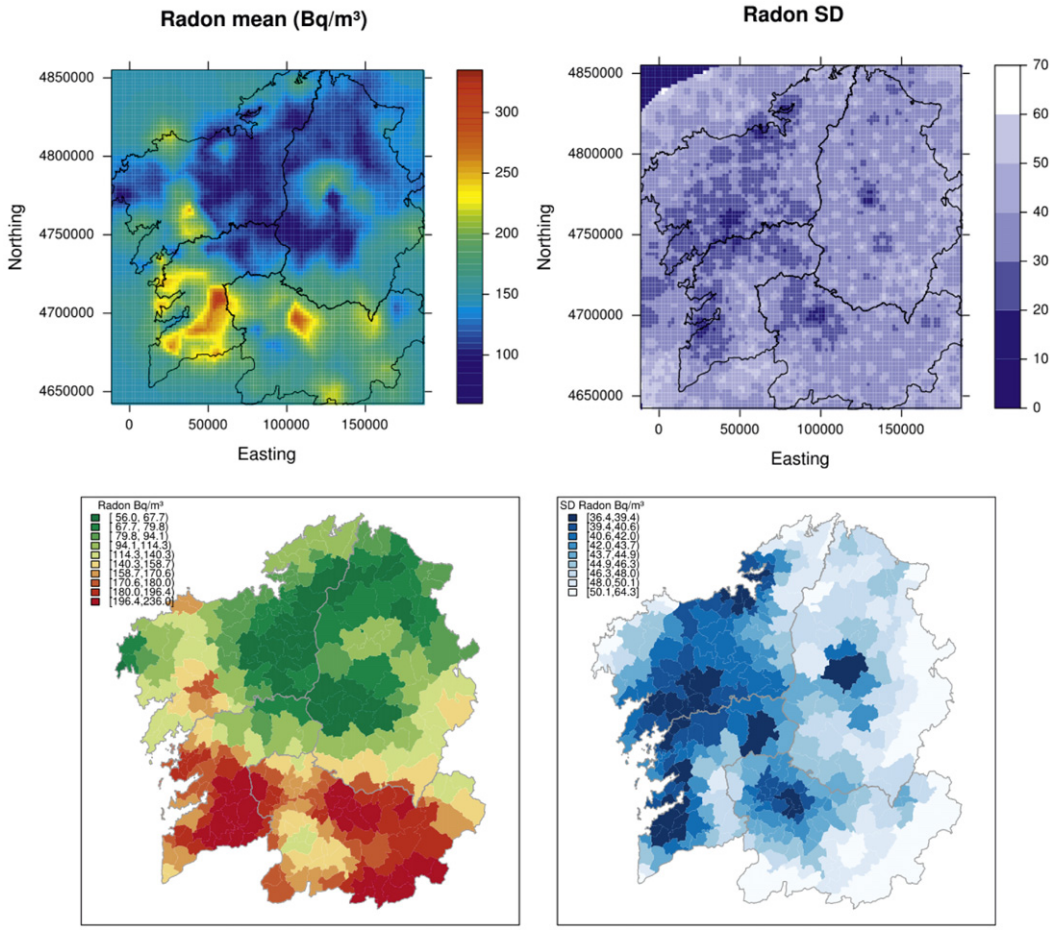



**Fig. 2.** Estimation of radon levels (left column) and its precision (right column) in Galician homes, on the estimation grid (upper row) and in municipalities (lower row): estimation based on the SPDE-INLA model.

intensity into account. The maps in the right hand column show the precision of the estimates (Krainski et al., 2016).

Table 3 shows the change in RRs of mortality, along with their 95% credibility intervals (CIs), for twofold increase in indoor radon, for each of the tumors analyzed. The table is stratified by sex and shows the results from the four models. RRs with CIs that do not include unity are marked in bold.

The analysis adjusted for sociodemographic variables and arsenic in topsoil showed a statistical association between residential radon and lung, stomach and brain cancer. This association was observed in women only. The effect measure of radon was 1.17 (95% CI 1.02, 1.32) in stomach cancer and 1.28 (95% CI 1.13, 1.50) in brain cancer. This RR indicates the increase in mortality for a twofold increase in exposure, e.g., in the case of lung cancer mortality in women, the RR was 1.09 (95% CI 1.00, 1.23).

Fig. 3 shows the municipal distribution of lung, stomach and brain cancer mortality in men and women in Galicia. Whereas the spatial pattern of stomach cancer mortality was very similar for men and women alike, lung and brain cancer mortality patterns differed between the sexes.

## 4. Discussion

Our results suggest that radon concentration in the interior of homes in Galicia is statistically associated with higher lung, stomach and brain cancer mortality among women. In men, however, no association with any tumor was found.

The choice of Galicia for carrying out this study is highly relevant for a number of reasons. First, owing to the region's geologic structure, it is an area with high radon levels, thereby making it the ideal place for studies seeking to model the dose-response between radon and the appearance of neoplasms. In other places where these types of studies have been conducted, radon concentrations are low, thus making observation of an effect more difficult (Bräuner et al., 2013). Second, the local population tends to live longer in the same home, better fitting our study's assumptions of chronic exposure. The median duration of residence was around 30 years in the same dwelling, something that does not tend to occur in the English-speaking world (Torres-Durán et al., 2014b).

The asymmetry between men and women in the results warrants comment. This was most noteworthy in the case of lung and, possibly, stomach cancer, since excess risk was solely detected in women, and both of these are tumors associated with smoking habit. Tobacco use may conceivably be the principal factor masking these associations. Among women in Spain, the generations that entered the ranks of smokers were those born from the 1940s onwards, so that our results in women are of special relevance, inasmuch as they included cohorts that had not smoked (López-Abente et al., 1995). Another component of the explanation might lie in the fact that, in Galicia, women tend to spend more time indoors (housewives) (Torres-Durán et al., 2014b) and to consume more water than do men (Mateos et al., 2002). This phenomenon, consisting in the fact that risk is detected solely in non-smokers, is a constant in the study of the relationship between cancer and radon, there being a high number of studies which focus on non-smokers. Different studies have indicated that radon also causes lung cancer in never smokers, as is the case of the pooled analyses performed by European (Darby et al., 2005) and North American authors (Krewski et al., 2005). Similarly, recent studies on never-smokers in Galicia indicate that there is a higher risk of lung cancer above 200 Bq/m$^3$ (Torres-Durán et al., 2014b); and a recent review of available studies

**Table 3**
Indoor radon and cancer mortality for different tumor sites, relative risk and 95% credibility intervals for a twofold increase in exposure: results from four geospatial regression models for misaligned data.

| Men | Unadjusted | | Soc | | Soc + As | | Soc + As + altitude | |
|---|---|---|---|---|---|---|---|---|
| | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI |
| Lung | 0.958 | 0.886, 1.037 | 0.98 | 0.910, 1.057 | 0.984 | 0.914, 1.057 | 0.973 | 0.906, 1.043 |
| Buccal cavity and pharynx | 1.074 | 0.946, 1.219 | 1.043 | 0.919, 1.189 | 1.036 | 0.914, 1.179 | 1.039 | 0.914, 1.181 |
| Oesophagus | 0.983 | 0.839, 1.121 | 0.988 | 0.894, 1.100 | 0.977 | 0.885, 1.086 | 0.984 | 0.890, 1.091 |
| Stomach | 1.083 | 0.952, 1.206 | 1.092 | 0.979, 1.219 | 1.098 | 0.991, 1.224 | 1.084 | 0.977, 1.206 |
| Pancreas | 1.029 | 0.912, 1.152 | 1.032 | 0.924, 1.161 | 1.038 | 0.925, 1.152 | 1.009 | 0.919, 1.095 |
| Colorectal | 0.978 | 0.918, 1.054 | 0.988 | 0.930, 1.060 | 0.995 | 0.936, 1.061 | 0.993 | 0.935, 1.060 |
| Prostate | 0.92 | 0.848, 0.988 | 0.94 | 0.859, 1.018 | 0.943 | 0.869, 1.011 | 0.940 | 0.864, 1.009 |
| Bladder | 0.93 | 0.795, 1.041 | 0.95 | 0.856, 1.053 | 0.951 | 0.858, 1.060 | 0.946 | 0.875, 1.053 |
| Kidney | 1.092 | 0.903, 1.285 | 1.131 | 0.989, 1.292 | 1.129 | 0.984, 1.284 | 1.122 | 0.980, 1.279 |
| Brain | 1.042 | 0.932, 1.160 | 1.039 | 0.924, 1.169 | 1.044 | 0.928, 1.172 | 1.045 | 0.930, 1.175 |
| Thyroid | 1.168 | 0.824, 1.630 | 1.086 | 0.755, 1.570 | 1.048 | 0.726, 1.534 | 1.046 | 0.721, 1.529 |
| NHL | 0.987 | 0.870, 1.096 | 1.060 | 0.937, 1.179 | 1.039 | 0.929, 1.162 | 1.036 | 0.927, 1.160 |
| Leukemias | 0.946 | 0.853, 1.052 | 0.969 | 0.865, 1.079 | 0.960 | 0.861, 1.071 | 0.951 | 0.856, 1.069 |
| Women | Unadjusted | | Soc | | Soc + As | | Soc + As + altitude | |
| | RR | 95% CI | RR | 95% CI | RR | 95% CI | RR | 95% CI |
| Lung | 1.087 | 0.977, 1.276 | **1.100** | **1.004, 1.232** | **1.101** | **1.008, 1.231** | **1.094** | **1.000, 1.231** |
| Buccal cavity and pharynx | 1.122 | 0.918, 1.367 | 1.091 | 0.872, 1.342 | 1.075 | 0.864, 1.322 | 1.068 | 0.857, 1.314 |
| Oesophagus | 1.110 | 0.873, 1.391 | 1.087 | 0.834, 1.410 | 1.075 | 0.837, 1.365 | 1.059 | 0.828, 1.353 |
| Stomach | **1.142** | **1.001, 1.301** | **1.185** | **1.039, 1.339** | **1.182** | **1.037, 1.334** | **1.174** | **1.022, 1.325** |
| Pancreas | 0.996 | 0.868, 1.132 | 1.017 | 0.894, 1.159 | 1.020 | 0.900, 1.157 | 0.999 | 0.889, 1.119 |
| Colorectal | 0.970 | 0.959, 0.978 | 0.997 | 0.935, 1.062 | 0.99 | 0.931, 1.054 | 0.991 | 0.932, 1.056 |
| Breast | 0.967 | 0.877, 1.065 | 0.970 | 0.872, 1.056 | 0.968 | 0.869, 1.040 | 0.963 | 0.871, 1.034 |
| Bladder | 1.128 | 0.904, 1.391 | **1.172** | **1.008, 1.381** | 1.139 | 0.976, 1.332 | 1.130 | 0.969, 1.323 |
| Kidney | 1.041 | 0.870, 1.262 | 1.137 | 0.949, 1.419 | 1.117 | 0.933, 1.375 | 1.113 | 0.916, 1.375 |
| Brain | **1.220** | **1.205, 1.244** | **1.305** | **1.147, 1.547** | **1.285** | **1.130, 1.495** | **1.283** | **1.128, 1.498** |
| Thyroid | 0.889 | 0.687, 1.164 | 0.949 | 0.729, 1.234 | 0.944 | 0.721, 1.236 | 0.95 | 0.733, 1.240 |
| NHL | 1.099 | 0.954, 1.277 | 1.100 | 0.939,1.236 | 1.072 | 0.875, 1.217 | 1.066 | 0.868, 1.211 |
| Leukemias | 1.004 | 0.894, 1.122 | 1.032 | 0.915, 1.165 | 1.040 | 0.927, 1.187 | 1.054 | 0.933, 1.191 |

RR 95% CI: relative risk and 95% credibility interval.
Unadjusted. Radon as explanatory variable.
Soc: Radon adjusted for sociodemographic variables.
Soc + As: Radon adjusted for sociodemographic variables and arsenic topsoil levels.
Soc + As + altitude: Radon adjusted for sociodemographic variables, arsenic topsoil levels, and altitude.

suggests a possible relationship between residential radon exposure and lung cancer risk in never-smokers (Torres-Durán et al., 2014a).

Another important area of discordance is brain cancer in men and women and its relationship with radon. Since central nervous system (CNS) tumors are associated with ionizing radiation, it is biologically plausible that residential radon might increase the risk of such tumors. Exposure to ionizing radiations has been shown to increase the risk of CNS tumors in children and adolescents exposed to computed tomography scans (Mathews et al., 2013). However, the results published are controversial and there are few general population studies. A Danish cohort study observed a statistically significant association between residential radon and CNS tumors (Bräuner et al., 2013) but another important cohort study showed no association between mean county radon levels and CNS tumor mortality (Turner et al., 2012a). Unfortunately, these studies do not furnish data stratified by sex and smoking status. A recent study, also undertaken in Galicia but using a different methodology, shows a correlation between CNS cancer mortality and indoor radon (Ruano-Ravina et al., 2017).

In the case of radon risk, the limitations of ecologic studies are particularly serious because of the presence of smoking, which constitutes an overarching risk factor for lung-cancer. As noted above, cigarette smoking causes a 1000 to 2000% excess risk of lung-cancer (NRCC-BEIR, 1999). Even so, smoking probably does not act as a confounding variable in the relationship between residential radon and lung cancer (and possibly other cancers), since it is not known if residential radon exposure is associated with smoking. Smoking acts as a strong effect modifier, and a submultiplicative interaction has been shown between radon exposure and smoking (Barros-Dios et al., 2002; Barros-Dios et al., 2012).

In exposure to indoor radon, the bronchial epithelium would presumably be the tissue that received the highest dose of ionizing radiation, yet the upper respiratory tract and skin would also be exposed, along with other organs, such as the kidneys and bone marrow. Furthermore, ingestion of water containing dissolved radon would entail exposure of the stomach and other organs of the digestive system (Kendall and Smith, 2002). River water is commonly used for supplying medium- and large-sized urban areas, while groundwater is used in lightly populated and rural areas as well as in individual dwellings and small industries. Galicia possesses a fractured soil rich in uranium-238 ($^{238}$U), together with important water resources that act as transport, with a correlation between their radiologic content and the gamma exposure rate at the site where they were sampled. The radioactive content of water is also associated with the type of rock with which it comes into contact (Llerena et al., 2013). The results of different studies undertaken in Galicia - including a prospective study, albeit with few subjects - also point in this direction, particularly for stomach cancer (Barbosa-Lorenzo et al., 2016; Barbosa-Lorenzo et al., 2017).

This analysis includes the greater part of the indoor radon measurements taken in Galicia. Spatial analysis, based on models which include radon levels and As content at their original sampling points as opposed to the location of the municipal centroid (misaligned data), takes into account the error of interpolation, an aspect not contemplated by

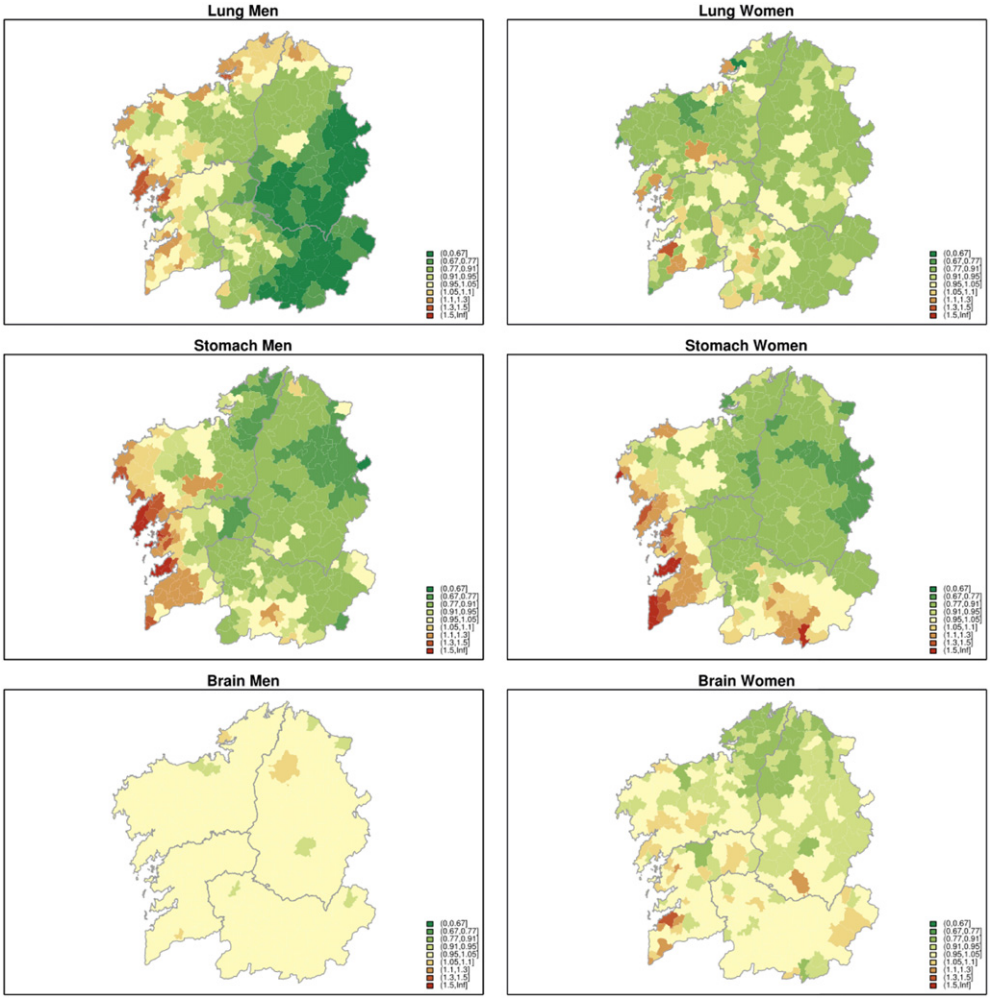



**Fig. 3.** Municipal distribution of stomach, lung and brain cancer mortality in Galicia, Spain. BYM modeling of mortality in men and women across a ten-year period. The maps depict the posterior mean relative risk (RR) for every town. Reference rates Galicia. Galicia 1999–2008.

kriging-based estimation. Moreover, such analysis includes the modeling of mortality with the BYM model, and is regarded as achieving high specificity (Richardson et al., 2004).

This type of study design is prone to the presence of the problem known as "preferential sampling". In some studies the degree of sampling depends on the response. For example, it is more common to have stations collecting data on pollution in industrial than in rural areas. Sampling should not depend on the response, and in our case there is no apparent relationship between the distribution of the sampling points and radon levels (Fig. 1). Nonetheless, a check was carried out to determine whether there was a preferential sampling issue in the data. To this end, we used a joint model for the sampling point pattern and the response (Diggle et al., 2010). No significant relationship was observed between the proportion of population sampling points (samples/habitants) and the response random field (radon levels).

The results shown in Table 3 illustrate the importance of confounding effects in the analysis of radon. Adjustment for sociodemographic variables, altitude, and As content in soil is another of the strengths of this study. The inclusion of As as a confounder in the evaluation of radon has been addressed in some miner cohort and case-control studies (Yao et al., 1994; Kusiak et al., 1993). There is also a tendency to have higher indoor radon concentration with altitude (Kropat et al., 2014).

In terms of study limitations, it has to be said that this was an ecologic mortality study and that we lacked data on tobacco use in this population. Another limitation lies in the fact that the number of radon measurements was relatively low (3371) and that these were heterogeneously distributed among the different geographical entities, though this heterogeneity was taken into account in the sampling. The use of current measures as an indicator of radon exposure, assuming stable home occupation for many years, could be an important limitation, though in our case the assumption was in great measure fulfilled. The use of mortality as an outcome is influenced by the different relative survival rates of the respective tumors, though for lung, stomach and brain cancer these are very low, i.e., 10.7%, 25% and 20%, respectively (De Angelis et al., 2014; Visser et al., 2015).

In 1999 the BEIR VI committee was of the opinion that ecologic studies of indoor-radon exposure and lung cancer were essentially noninformative and shed little light on the association between indoor radon-progeny exposure and lung cancer (NRCC-BEIR, 1999). However, our results suggest that exposure to indoor radon and other related environmental agents (e.g., water with high radon levels) might have a role in the etiology of tumors other than lung cancer, at least in Galicia. This result is not an isolated one, since it is in line with those reported in analytic studies with different designs conducted on the same population.

In conclusion, the results show that a higher concentration of indoor residential radon in Galicia is statistically associated with higher lung, stomach and brain cancer mortality in women. These associations are biological plausible, and the results of other studies conducted on the same population point in this same direction, particularly in the case of stomach cancer. With respect to the relationship between radon and brain and stomach cancer, further analytic epidemiological studies are needed to confirm these results, and an assessment should be made of the advisability of implementing interventions targeting such exposure in higher-risk areas.

## Acknowledgements

The study was partially supported by research grants from the Carlos III Health Institute (PI4CIII/50) and Spanish Health Research Fund (FIS PI11/00871). Mortality data were supplied by the Spanish National Statistics Institute in accordance with a specific confidentiality protocol.

## References

Barbosa-Lorenzo, R., Barros-Dios, J.M., Raíces Aldrey, M., Cerdeira Caramés, S., Ruano-Ravina, A., 2016. Residential radon and cancers other than lung cancer: a cohort study in Galicia, a Spanish radon-prone area. Eur. J. Epidemiol. 31:437–441. http://dx.doi.org/10.1007/s10654-016-0134-x.

Barbosa-Lorenzo, R., Barros-Dios, J.M., Ruano-Ravina, A., 2017. Radon and stomach cancer. Int. J. Epidemiol. http://dx.doi.org/10.1093/ije/dyx011.

Barros-Dios, J.M., Barreiro, M.A., Ruano-Ravina, A., Figueiras, A., 2002. Exposure to residential radon and lung cancer in Spain: a population-based case-control study. J Epidemiol]–>Am. J. Epidemiol. 156, 548–555.

Barros-Dios, J.M., Ruano-Ravina, A., Pérez-Ríos, M., Castro-Bernárdez, M., Abal-Arca, J., Tojo-Castro, M., 2012. Residential radon exposure, histologic types, and lung cancer risk. A case-control study in Galicia, Spain. Cancer Epidemiol. Biomark. Prev. 21: 951–958. http://dx.doi.org/10.1158/1055-9965.EPI-12-0146-T.

Besag, J., York, J., Mollié, A., 1991. Bayesian image restoration with two applications in spatial statistcs. Ann. Inst. Stat. Math. 43, 1–59.

Bräuner, E.V., Andersen, Z.J., Andersen, C.E., Pedersen, C., Gravesen, P., Ulbak, K., Hertel, O., Loft, S., Raaschou-Nielsen, O., 2013. Residential radon and brain tumour incidence in a Danish cohort. PLoS One 8, e74435. http://dx.doi.org/10.1371/journal.pone.0074435.

Darby, S., Hill, D., Auvinen, A., Barros-Dios, J.M., Baysson, H., Bochicchio, F., Deo, H., Falk, R., Forastiere, F., Hakama, M., Heid, I., Kreienbrock, L., Kreuzer, M., Lagarde, F., Makelainen, I., Muirhead, C., Oberaigner, W., Pershagen, G., Ruano-Ravina, A., Ruosteenoja, E., Rosario, A.S., Tirmarche, M., Tomasek, L., Whitley, E., Wichmann, H.E., Doll, R., 2005. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. BMJ 330, 223.

De Angelis, R., Sant, M., Coleman, M.P., Francisci, S., Baili, P., Pierannunzio, D., Trama, A., Visser, O., Brenner, H., Ardanaz, E., Bielska-Lasota, M., Engholm, G., Nennecke, A., Siesling, S., Berrino, F., Capocaccia, R., EUROCARE-5 Working Group, 2014. Cancer survival in Europe 1999–2007 by country and age: results of EUROCARE—5-a population-based study. Lancet Oncol. 15:23–34. http://dx.doi.org/10.1016/S1470-2045(13)70546-1.

Diggle, P.J., Menezes, R., Su, T., 2010. Geostatistical inference under preferential sampling. C Appl. Stat.]–>J. R. Stat. Soc.: Ser. C: Appl. Stat. 59:191–232. http://dx.doi.org/10.1111/j.1467-9876.2009.00701.x.

Finley, A.O., Banerjee, S., Cook, B.D., 2014. Bayesian hierarchical models for spatially misaligned data in R. Methods Ecol. Evol. 5:514–523. http://dx.doi.org/10.1111/2041-210X.12189.

Gotway, C.A., Young, L.J., 2002. Combining incompatible spatial data. J. Am. Stat. Assoc. 97: 632–648. http://dx.doi.org/10.1198/016214502760047140.

Gutierrez-Villanueva, J.L., Sainz-Fernández, C., Fuente-Merino, I., Sáez-Vergara, J.C., Correa-Garcés, E., Quindos-Poncela, L.S., 2013. Intercomparison exercise on external gamma dose rate under field conditions at the laboratory of natural radiation (Saelices el Chico, Spain). Radiat. Prot. Dosim. 155:459–466. http://dx.doi.org/10.1093/rpd/nct016.

Kendall, G.M., Smith, T.J., 2002. Doses to organs and tissues from radon and its decay products. J. Radiol. Prot. 22, 389–406.

Krainski, E.T., Lindgren, F., Simpson, D., Rue, H., 2016. The R-INLA Tutorial on SPDE Models.

Krewski, D., Lubin, J.H., Zielinski, J.M., Alavanja, M., Catalan, V.S., Field, R.W., Klotz, J.B., Létourneau, E.G., Lynch, C.F., Lyon, J.I., Sandler, D.P., Schoenberg, J.B., Steck, D.J., Stolwijk, J.A., Weinberg, C., Wilcox, H.B., 2005. Residential radon and risk of lung cancer: a combined analysis of 7 North American case-control studies. Epidimiology 16, 137–145.

Kropat, G., Bochud, F., Jaboyedoff, M., Laedermann, J.-P., Murith, C., Palacios, M., Baechler, S., 2014. Major influencing factors of indoor radon concentrations in Switzerland. J. Environ. Radioact. 129:7–22. http://dx.doi.org/10.1016/j.jenvrad.2013.11.010.

Kusiak, R.A., Ritchie, A.C., Muller, J., Springer, J., 1993. Mortality from lung cancer in Ontario uranium miners. Br. J. Ind. Med. 50, 920–928.

Lindgren, F., Rue, H., 2015. Bayesian spatial modelling with R-INLA. J. Stat. Softw. 63, 1–25.

Lindgren, F., Rue, H., Lindström, J., 2011. An explicit link between gaussian fields and gaussian markov random fields: the stochastic partial differential equation approach. J. R. Stat. Soc. Ser. B Stat Methodol. 73:423–498. http://dx.doi.org/10.1111/j.1467-9868.2011.00777.x.

Llerena, J.J., Cortina, D., Durán, I., Sorribas, R., 2013. Impact of the geological substrate on the radiological content of Galician waters. J. Environ. Radioact. 116:48–53. http://dx.doi.org/10.1016/j.jenvrad.2012.08.014.

Locutura, J., Bel-Lan, A., Garcia Cortés, A., Martínez Romero, S., 2012. Atlas geoquímico de España. Instituto Geológico y Minero de España, Madrid.

López-Abente, G., Pollán, M., de la Iglesia, P., Ruiz, M., 1995. Characterization of the lung cancer epidemic in the European Union (1970–1990). Cancer Epidemiol. Biomark. Prev. 4, 813–820.

López-Abente, G., Aragonés, N., Ramis, R., Hernandez-Barrera, V., Pérez-Gómez, B., Escolar-Pujolar, A., Pollán, M., 2006. Municipal distribution of bladder cancer mortality in Spain: possible role of mining and industry. BMC Public Health 6, 17.

Marsh, J.W., Blanchardon, E., Gregoratto, D., Hofmann, W., Karcher, K., Nosske, D., Tomásek, L., 2012. Dosimetric calculations for uranium miners for epidemiological studies. Radiat. Prot. Dosim. 149:371–383. http://dx.doi.org/10.1093/rpd/ncr310.

Mateos, R., Páramo, M., Carrera, I., Rodríguez-López, A., 2002. Alcohol consumption in a southern European region (Galicia, Spain). Subst. Use Misuse 37, 1957–1976.

Mathews, J.D., Forsythe, A.V., Brady, Z., Butler, M.W., Goergen, S.K., Byrnes, G.B., Giles, G.G., Wallace, A.B., Anderson, P.R., Guiver, T.A., McGale, P., Cain, T.M., Dowty, J.G., Bickerstaffe, A.C., Darby, S.C., 2013. Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. BMJ 346, f2360.

Miles, J.C.H., Cliff, K.D., 1992. Dose to lung and other organs from radon and thoron as a function of age. Radiat. Prot. Dosim. 41:251–253. http://dx.doi.org/10.1093/oxfordjournals.rpd.a081263.

NCRP, 1984. Evaluation of Occupational and Environmental Exposures to Radon and Radon Daughters in the United States, NCRP REPORT. Bethesda, Md.

NRCC-BEIR, 1999. Health Effects of Exposure to Radon: BEIR VI. National Academic Press, Washington DC.

Nuñez, O., Fernández-Navarro, P., Martín-Méndez, I., Bel-Lan, A., Locutura, J., López-Abente, G., 2016. Arsenic and chromium topsoil levels and cancer mortality in Spain. Environ. Sci. Pollut. Res. Int. 23 (17), 17664–17675.

Quindos, L.S., Fernandez, P.L., Sainz, C., Fuente, I., Nicolas, J., Quindos, L., Arteche, J., 2008. Indoor radon in a Spanish region with different gamma exposure levels. J. Environ. Radioact. 99, 1544–1547.

Richardson, S., Thomson, A., Best, N., Elliott, P., 2004. Interpreting posterior relative risk estimates in disease-mapping studies. Environ. Health Perspect. 112, 1016–1025.

Ruano-Ravina, A., Aragones, N., Kelsey, K.T., Pérez-Ríos, M., López-Abente, G., Barros-Dios, J.M., 2017. Residential radon exposure and brain tumors. An ecological study in a radon prone area (Galicia, Spain). Sci. Rep. 7 (1), 3595.

Rue, H., Martino, S., 2010. The R-INLA project. URL. http://www.r-inla.org/, Accessed date: 10 August 2010 (WWW Document).

Rue, H., Martino, S., Chopin, N., 2009. Approximate Bayesian inference for latent Gaussian models by using integrated nested Laplace approximations. J. R. Stat. Soc. Ser. B 71: 319–392. http://dx.doi.org/10.1111/j.1467-9868.2008.00700.x.

Sainz Fernández, C., Quindós Poncela, L.S., Fernández Villar, A., Fuente Merino, I., Gutierrez-Villanueva, J.L., Celaya González, S., Quindós López, L., Quindós López, J., Fernández, E., Remondo Tejerina, J., Martín Matarranz, J.L., García Talavera, M., 2017. Spanish experience on the design of radon surveys based on the use of geogenic information. J. Environ. Radioact. 166:390–397. http://dx.doi.org/10.1016/j.jenvrad.2016.07.007.

Schüz, J., Espina, C., Villain, P., Herrero, R., Leon, M.E., Minozzi, S., Romieu, I., Segnan, N., Wardle, J., Wiseman, M., Belardelli, F., Bettcher, D., Cavalli, F., Galea, G., Lenoir, G., Martin-Moreno, J.M., Nicula, F.A., Olsen, J.H., Patnick, J., Primic-Zakelj, M., Puska, P., van Leeuwen, F.E., Wiestler, O., Zatonski, W., Working Groups of Scientific Experts, 2015. European Code Against Cancer 4th Edition: 12 ways to reduce your cancer risk. Cancer Epidemiol. 39 (Suppl. 1):S1–10. http://dx.doi.org/10.1016/j.canep.2015.05.009.

Torres-Durán, M., Barros-Dios, J.M., Fernández-Villar, A., Ruano-Ravina, A., 2014a. Residential radon and lung cancer in never smokers. A systematic review. Cancer Lett. 345:21–26. http://dx.doi.org/10.1016/j.canlet.2013.12.010.

Torres-Durán, M., Ruano-Ravina, A., Parente-Lamelas, I., Leiro-Fernández, V., Abal-Arca, J., Montero-Martínez, C., Pena-Álvarez, C., González-Barcala, F.J., Castro-Añón, O., Golpe-Gómez, A., Martínez, C., Mejuto-Martí, M.J., Fernández-Villar, A., Barros-Dios, J.M., 2014b. Lung cancer in never-smokers: a case-control study in a radon-prone area (Galicia, Spain). Eur. Respir. J. 44:994–1001. http://dx.doi.org/10.1183/09031936.00017114.

Turner, M.C., Krewski, D., Chen, Y., Pope, C.A., Gapstur, S.M., Thun, M.J., 2012a. Radon and nonrespiratory mortality in the American Cancer Society cohort. Am. J. Epidemiol. 176:808–814. http://dx.doi.org/10.1093/aje/kws198.

Turner, M.C., Krewski, D., Chen, Y., Pope, C.A., Gapstur, S.M., Thun, M.J., 2012b. Radon and COPD mortality in the American Cancer Society Cohort. Eur. Respir. J. 39:1113–1119. http://dx.doi.org/10.1183/09031936.00058211.

USNRC, 1999. Risk Assessment of Radon in Drinking Water. National Academy Press, Washington DC.

Vargas, A., Ortega, X., 2006. Influence of environmental changes on continuous radon monitors. Results of a Spanish intercomparison exercise. Radiat. Prot. Dosim. 121: 303–309. http://dx.doi.org/10.1093/rpd/ncl036.

Vargas, A., Ortega, X., 2007. Influence of environmental changes on integrating radon detectors: results of an intercomparison exercise. Radiat. Prot. Dosim. 123:529–536. http://dx.doi.org/10.1093/rpd/ncl161.

Visser, O., Ardanaz, E., Botta, L., Sant, M., Tavilla, A., Minicozzi, P., EUROCARE-5 Working Group, 2015. Survival of adults with primary malignant brain tumours in Europe; results of the EUROCARE-5 study. Eur. J. Cancer 1990. http://dx.doi.org/10.1016/j.ejca.2015.07.032.

Yao, S.X., Lubin, J.H., Qiao, Y.L., Boice, J.D., Li, J.Y., Cai, S.K., Zhang, F.M., Blot, W.J., 1994. Exposure to radon progeny, tobacco use and lung cancer in a case-control study in southern China. Radiat. Res. 138, 326–336.

Zeeb, H., Shannoun, F., 2009. WHO Handbook on Indoor Radon: A Public Health Perspective. WHO, Geneva.