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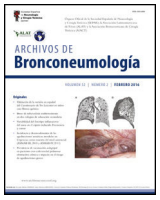

Original Article

Radon, Tobacco Exposure and Non-Small Cell Lung Cancer Risk Related to BER and NER Genetic Polymorphisms☆

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ABSTRACT

Introduction: Tobacco consumption and radon exposure are considered the first and second most common causes of lung cancer, respectively. The aim of this study was to analyze both whether selected genetic polymorphisms in loci that are in DNA repair pathways, are related to non-small-cell lung cancer (NSCLC) and whether they may modulate the association between residential radon exposure and lung cancer in both smokers and never smokers.
Methods: A multicentre, hospital-based, case–control study with 826 cases and 1201 controls was designed in a radon-prone area. Genotyping was determined in whole blood and residential radon exposure was measured in participants' dwellings.
Results: Attending to tobacco exposure, the variant in the gene *NBN* (rs1805794) was associated with lung cancer in never smokers (OR 2.72; 95%1.44–5.2) and heavy smokers (OR 3.04; 95%CI 1.21–7.69). The polymorphism with the highest lung cancer association was *OGG1* (rs125701), showing an OR of 8.04 (95%CI 1.64–58.29) for its homozygous variant genotype in heavy smokers. Attending to indoor radon exposure (>200 Bq/m^3), rs1452584, for its homozygous variant genotype, showed the highest association (OR 3.04 (95%CI 1.15–8.48).
Conclusion: The genes analyzed seem to have no association with the fully adjusted model, but they might modulate lung cancer association when different categories of tobacco consumption are considered (i.e. heavy smokers). This association may similarly be elevated for those individuals having high indoor radon exposures, though at a minor extent.

El radón, la exposición al tabaco y el riesgo de desarrollar cáncer de pulmón de células no pequeñas en relación con polimorfismos genéticos de BER y NER

Palabras clave:
Cáncer de pulmón de células no pequeñas
Fumadores
No fumadores

RESUMEN

Introducción: El consumo de tabaco y la exposición al radón se consideran la primera y la segunda causa más frecuentes de cáncer de pulmón, respectivamente. El objetivo de este estudio fue analizar si determinados polimorfismos genéticos en los *loci* que forman parte de la cascada de reparación del ADN se asocian con el cáncer de pulmón de célula no pequeña, y también si es posible que modifiquen la

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Polimorfismos genéticos
Radón

asociación entre la exposición al radón en el hogar y el cáncer de pulmón tanto en fumadores como en no fumadores.
Métodos: Se diseñó un estudio multicéntrico hospitalario de casos y controles con 826 casos y 1.201 controles en un área proclive a la presencia de radón. Se determinó el genotipo en sangre y se midió la exposición al radón en el lugar de residencia de los participantes.
Resultados: Analizando la exposición al tabaco, la variante del gen *NBN* (rs1805794) se asoció con el cáncer de pulmón en no fumadores (OR 2,72; IC 95% 1,44-5,2) y grandes fumadores (OR 3,04; IC 95% 1,21-7,69). El polimorfismo con mayor asociación con el cáncer de pulmón fue *OGG1* (rs125701), con una OR de 8,04 (IC 95% 1,64-58,29) para la variante genotípica en homocigosis en grandes fumadores. En cuanto a la exposición al radón en interiores (> 200 Bq/m^3), rs1452584 en homocigosis mostró la asociación más fuerte (OR 3,04; IC 95% 1,15-8,48).
Conclusión: Los genes que se analizaron no muestran asociación con el modelo completamente ajustado, pero podrían modificar la asociación con el cáncer de pulmón cuando se consideran diferentes categorías de consumo de tabaco (esto es, grandes fumadores). Esta asociación podría aumentar de forma similar en aquellos individuos que están expuestos al radón en interiores, aunque en menor medida.

Introduction

Worldwide, lung cancer represents 11.4% of overall cancer diagnoses. It is also the leading cause of cancer death, accounting for 18% of all cancer deaths. It is the most frequently occurring cancer among men and the third most frequent in women. Lung cancer is the leading cause of cancer death among men and the second most common fatal cancer in women, comprising 21.5 and 13.7% of all cancer deaths, respectively.[1,2] Tobacco consumption is the main association factor of this disease followed by exposure to indoor radon.[2]

Radon is classified as the main cause of lung cancer in never smokers and the second most common in ever-smokers by the United States Environmental Protection Agency (USEPA) and the World Health Organization (WHO).[3–5] The molecular mechanism of radon carcinogenesis is not fully understood, and lack of knowledge remains regarding the precise molecular carcinogenic pathways for tobacco exposure. Genetic susceptibility may play an important role and explains why some people develop lung cancer and others do not, given the same tobacco or indoor radon exposures.[6,7]

Tobacco smoke, despite damaging DNA, has an additional effect in DNA repair pathway activity, reducing the detectable amount of some repair proteins, (including XPC, OGG1 and OGG2) in pulmonary tissue in mouse models.[8] Tobacco smoke exposure induces bulky DNA adducts, which have a linear relationship with carcinogenesis at low exposure, but with high doses may reach a steady state, possibly due to DNA repair pathway saturation and increased apoptosis.[9,10]

Low capacity in DNA repair is related with an increased association with lung cancer.[11,12] There are three major types of DNA repair mechanisms: nucleotide excision repair (NER), the main route in mammals which repair DNA damaged by ultraviolet light, environmental mutagens and chemotherapy[12]; base excision repair (BER) that repairs DNA damaged by oxidation, deamination and alkylation. It protects from ageing, neurodegeneration and cancer[13]; and mismatch repair (MMR) that blocks recombination between non identical DNA.[14] Published studies have focused in genes involved in NER such as ERCC1 and ERCC2, BER such as XRCC1 and OGG1, and MMR such as XRCC3.[15] Nevertheless, no study has analyzed the potential interplay between these molecular pathways and indoor radon exposure.

The aim of this study was to analyze if selected genetic polymorphisms in genes playing a role in these molecular pathways are associated with an increased association of NSCLC. As a secondary objective, we have analyzed the effect of these genes taking into account the different amount of tobacco consumption and indoor radon exposure, to ascertain a potential modulating effect for the polymorphisms analyzed.

Subjects and methods

Design, subjects and settings

A multicentre, hospital-based, case–control study was conducted in 12 Spanish hospitals located in four different regions. The population was insured by the National Health Service. Lung cancer diagnosis was pathologically confirmed in their respective hospitals of reference. Cases and controls were recruited between January 2011 and October 2018. All patients had to be at least 30 years old, with no upper limit to participant age. Subjects with a previously history of cancer were excluded. To be included as a case, the patient had to have a pathologically confirmed primary lung cancer. Small Cell Lung Cancer patients were excluded. Controls were individuals undergoing minor, non-oncological, ambulatory surgery not related to tobacco consumption. Controls were recruited using frequency-based age and sex matching with cases in order to ensure a similar distribution between cases and controls. We have used this approach previously.[6,16] The study protocol was approved by the Santiago de Compostela Committee of Research Ethics (reference 2010/295 and 2013/364). Written informed consent was obtained for all participants.

Data collection and radon measurements

All participants answered a questionnaire administered through personal interview regarding their lifestyle, with especial emphases on smoking habit and indoor radon. A detailed smoking history was obtained through interview. Radon was measured in the dwellings of participants. The return rate of radon devices was higher than 87% for both cases and controls. The Galician Radon Laboratory (www.radon.gal; School of Medicine, University of Santiago de Compostela, Galicia, Spain) read the detectors. This is one of three laboratories certified by the National Entity of Accreditation to measure indoor radon ins Spain.

Laboratory methods

Twenty-four single nucleotide polymorphisms (SNP) in fifteen genes and one SNP in a non-protein-coding RNA (ncRNA) region of chromosome 18 involved in DNA repair were investigated. The genes analyzed involved in DNA repair were: *ERCC1* (rs11615, rs3212986), *ERCC2* (rs13181, rs1799793), *ERCC3* (rs3738948, rs4150459), *ERCC5* (rs1047768, rs2094258), *OGG1* (rs1052133, rs2072668, rs2472037, rs125701), *APEX1* (rs1130409, rs3136817), *XRCC1* (rs25487), *XRCC3* (rs861539), *MUTYH* (rs3219489), *NBN* (rs1805794), *RRM1* (rs12806698), *XPC*

(rs2228001), *KLH4* (rs5922437) and *FATS* (rs11245007). In addition, we included in this study the single-nucleotide variation in intronic region rs1452584, located in chromosome 18, q21.33, which is in a ncRNA gene, these regions might have regulatory functions.[17]

Genetic polymorphisms in the studied genes (were analyzed from DNA extracted from 3 ml of whole blood donated by the participants. Genotyping was performed at the CeGen, which is one of the three genotyping core facilities of the National Genotyping Centre (belonging to the University of Santiago de Compostela).

SNPs were studied with MassARRAY® System developed by Agena Bioscience Inc., a technology which make possible the investigation of the presence of punctual variants of DNA.[18]

Statistical analysis

A bivariate descriptive analysis was performed comparing the characteristics of cases and controls. We performed a multiple logistic regression in which the dependent variable was the case or control status of the participants and the main independent variables were the SNPs studied. Results were adjusted by age and sex in the first model. Tobacco consumption and indoor radon exposure were added to the previous variables creating a fully adjusted model. The homozygote polymorphism genotype of the common allele (wild type) was used as the reference group.

To assess the existence of a relationship between selected genetic polymorphisms and tobacco consumption, we stratified smoking habit in three categories (never smokers, moderate smokers (second tercile: 34–66 packs-years) and heavy smokers (third tercile: >66 packs-year) and each polymorphism in three different genotypes (homozygous for the common allele (wild type), heterozygous and homozygous for the mutation). In addition, we studied whether lung cancer association was modified between the same polymorphisms and radon indoor exposure stratifying this variable in two categories ($\leq$200 Bq/m^3 and >200 Bq/m^3). Stratification at 200 Bq/m^3 was applied since previous studies have demonstrated that the association of lung cancer was increased at this dose.[19,20] All statistical results are expressed as Odds Ratios (OR) with their 95% confidence intervals. Statistical analyses were performed with IBM SPSS v22 (IBM, Armonk, NY, USA). We included in the tables the *p*-values and we corrected them applying the False Discovery Rate because to reduce the possibility of false positive results due to multiple comparisons.

Results

The study included 2027 participants, 826 cases and 1201 controls. Cases and controls were well balanced regarding sociodemographic variables, with an average age of 65.5, 50.5% of women. Cases and controls lived a similar number of years in the same dwelling. Residential radon exposure was available for 754 cases (91.3%) and 1010 controls (84.1%). The most frequent histological type was adenocarcinoma (69.7%). A sample description broken down by case–control status is shown in Table 1.

Table 2 summarizes the results for the different genotypes and their distribution between cases and controls. Compared to participants with wild type gene *NBN* (rs1805794) showed an OR for the homozygous genotype of 1.78 (95%CI 1.23–2.58) and 1.78 (95%CI 1.15–2.75) after adjustment for age and sex and full adjustment, respectively. This result along other results for other polymorphisms showing no association are shown in Table 2.

Table 3 shows the association of the different polymorphisms studied with lung cancer at varying tobacco exposure categories (never-smokers, moderate-smokers and heavy-smokers). Lung cancer association increases when participants are heavy smokers for almost all the polymorphisms analyzed. Compared with never-smokers, the highest OR corresponded to homozygous genotype in heavy smokers for: *OGG1* (rs125701) (OR 8.04; 95%CI 1.64–58.29), *OGG1* (rs2472037) (OR 6.1; 95%CI 2.3–17.5) and *ERCC1* (rs32112986) (OR 5.92; 95%CI 1.59–28.18). Only *ERCC3* (rs4150459) in its homozygous type expressed an increased association with NSCLC in moderate smokers compared with never smokers with wild type (OR 2.9; 95%CI 1.96–4.33). *NBN* (rs1805794) in its homozygous genotype showed a higher association with lung cancer in never smokers (OR 2.72; 95%CI 1.44–5.2).

Table 4 shows the association of these polymorphisms with lung cancer broken down by radon concentration ($\leq$200 Bq/m^3 and >200 Bq/m^3). NSCLC associations were increased for some variants for those participants exposed to more than 200 Bq/m^3. rs1452584 showed the highest association for the homozygous genotype (OR 3.04; 95% CI 1.15–8.48) as well as *APEX1* (rs1130409) and *ERRC1* (rs11615) showed a higher association too (OR 1.68; 95% CI 1.04–2.73 and OR 1.65; 95%CI 1.1–2.48 respectively). *XRCC3* (rs861539), *ERCC2* (rs13181), *OGG1* (rs10521333) and *ERRC1* (rs3212986) showed this increase for the heterozygous form (OR 1.79; 95%CI 1.28–2.51, OR 1.56; 95%CI 1.13–2.15, OR 1.53; 95%CI 1.09–2.16 and OR 1.47; 95%CI 1.06–2.04, OR 1.47; 95% CI 1.06–2.04 respectively). In addition, NBN (rs1805794) showed an increased association for its homozygous genotype for low indoor radon exposures (OR 1.88; CI 95% (1.09–3.24). No other significant association was observed.

Discussion

We found that the association with lung cancer may be modulated by different genetic polymorphisms in the BER and NER pathways. These polymorphisms appear to have the most prominent effect when they are homozygous in heavy smokers. Some polymorphisms could also increase NSCLC association in those individuals exposed to high radon concentrations. To our knowledge, this is the study with the largest number of DNA repair genes analyzed involved in lung cancer related to radon exposure. It also provides potentially valuable data for further understanding of the carcinogenic pathway of tobacco consumption. The sample size of our study is large, with 2027 participants including smokers, never smokers and indoor radon exposure, and expands a previous study performed exclusively in never smokers.[7]

We have observed that participants considered heavy smokers, globally, had an increased association with lung cancer compared with the wild type in never smokers. The polymorphism most associated with NSCLC was rs125701 (*OGG1*) in its homozygous variant form. Attending to the study of Hualong Qin et al. this polymorphism is frequently methylated in NSCLC, but in that study no significant result was obtained. This could be due to the absence of homozygous participants for this gene. In contrast with our study, it was performed only in Chinese population.[21] A relevant association was also observed for rs2472037 and rs3212986, both in the *OGG1* gene, for its homozygous genotypes, increasing the association of lung cancer in heavy smokers. Regarding rs3212986, this polymorphism is considered an important contributor to lung cancer development in smokers.[22,23] In addition, no relation with never smokers was detected by Tau Yu et al.[23]

The *NBN* gene variant (rs1805794), located in MMR pathway, was also associated with an increased association with lung cancer in heavy smokers in accordance with Chuang et al.,[24] though they only found association in male smokers. The homozygous mutation of this gene in heavy smokers shows a higher lung cancer association compared to never smokers. These results are similar to the obtained by Charlotta et al.[25] who found an increased lung cancer association in never smoking women and smoking women with low tobacco consumption. The increased lung cancer

Table 1
Sample description broken down by case–control status.

Variable	Cases, *n* (%)	Controls, *n* (%)
Number of patients	826 (40.7%)	1201 (59.3%)
Median age (range)/25-75th percentile	67 (25–94)/59–74	64 (21–92)/56–72
Sex		
Female	417 (50.5)	553 (46)
Male	409 (49.5)	648 (54)
Education		
No formal studies	164 (20.3)	191 (16)
Primary School	402 (49.7)	609 (51.1)
High School	135 (16.7)	236 (19.8)
University degree	108 (13.3)	156 (13.1)
Tobacco consumption		
Never-smokers	428 (57.3)	708 (61.3)
Light smokers (first tertile, 1–33 pack-years)	86 (11.5)	266 (23)
Moderate smokers (second tertile, 34–66 pack-years)	132(17.7)	128 (11.1)
Heavy smokers (third tertile, >66 pack-years)	101 (13.5)	53 (4.6)
Residential radon exposure Bq/m^3		
≤100	190 (25.2)	300 (29.7)
101–147	141 (18.7)	210 (20.8)
148–199	116 (15.4)	155 (15.3)
≥200	307 (40.7)	345 (34.2)
Geometric mean (95% CI)	166.18 (156.94–175.96)	152.58 (145.18–160.36)
Median (25-75th percentiles)	164.5 (99.8–280.3)	146 (90.8–254.3)
Years (median) living in the measured dwelling/25–75th percentiles	28 (14–40)	30 (15–40)
Histological types		
Adenocarcinoma	573 (69.7)	
Squamous cell carcinoma	154 (18.7)	
Large cell carcinoma	29 (3.5)	
Other histological types	66 (8)	

association shown in our study is similar to that reported by the Wang et al. meta-analyses.[26] In contrast, He et al. did not find any similar association.[27] This gene is known to take part in other carcinogenic procedures such as ovarian, breast and colorectal cancer. In addition, it has been studied for clinical purposes in the testing of hereditary cancers.[28]

In general, our results note that a number of genetic polymorphisms are associated with increased lung cancer association when these polymorphisms are homozygous. This was apparent for a number of the analyzed genes, especially those in the NER pathway. This could be attributable to the importance of this pathway in the repair of bulky DNA lesions generated by environmental mutagens.[12] The gene which showed a clear increase in NSCLC, compared to the wild type in heavy smokers, belonging to this pathway is *ERRC1* (rs3212986). *OGG1* polymorphisms rs125701 and rs2472037 showed the same effect but they are located in the BER pathway, which is specialized in repairing adducts originated by oxidation.[13] This is one of the main routes through which tobacco smoke produces DNA adducts.[8,29] This is interesting because there seems to be no association when we analyze these polymorphisms in the overall sample. Nevertheless, when we stratify the sample by smoking categories, we observe that for heavy smokers an association is present for some homozygous polymorphisms, suggesting a saturation effect on the anticarcinogenic pathways compared to wild type genes.

In relation with indoor radon exposure, we observed that participants exposed to more than 200 Bq/m^3 showed an increased lung cancer association for some of the polymorphisms studied. Only three of them showed an increased lung cancer association for their homozygous genotype: rs1452584, located in chromosome 18, showed the highest association; *ERCC1* (rs11615), located in NER pathway, which also showed an increased association for its wild type and *APEX1* (rs1130409), located in BER pathway. The results obtained for *ERCC1* are in accordance to the obtained by Lorenzo-González et al.[8] though this study is limited to a never smoking population while ours includes also ever-smokers. Other polymorphisms showed higher association for their heterozygous genotype; one of them, located in the NER pathway, *ERCC1* (rs3212986) showed similar results to those found by Lorenzo-Gonzalez et al.[7]

Despite the fact that some studies established a relationship between lung cancer association and DNA repair genes,[22,30] we are not aware of any study relating these polymorphisms with indoor radon exposure. These findings support our hypothesis that lung cancer association is increased by indoor radon exposure and that some variants might have a special importance favouring the development of this disease.

This research has some limitations. The most important limitation is that when we correct the *p*-value with the false discovery rate, we observed that some "suggestive" *p*-values in different genes become "non-suggestive", but it is important to resemble that a "non-suggestive" association cannot be deduced only by a *p*-value because it could be easily modified. For example, if we have a small number of participants in one category, we might have a "non-suggestive" *p*-value and a suggestive confidence interval. If we increase the number of participants in the category we could have a significant *p*-value while the width of the confidence interval narrows. Secondly, we did not have enough participants in some polymorphisms, which makes difficult to establish a potential association with lung cancer. One example is ERCC3 (rs4150459) that for its homozygous genotype for never-smokers did not have enough participants to obtain any result. Other limitations reside in the limited number of polymorphisms we have assessed. Not all polymorphisms present in the studied genes have been analyzed, and the BER and NER pathways have some more genes that we do not have analyzed. A further limitation is the fact that there are other pathways and genes involved in carcinogenesis that we do not have included and might have a role, such as deletion of GSTM1 and GSTT1 genes.[31] Finally, the most frequent histological type was adenocarcinoma. This is due to the fact that we included an

Table 2
Lung cancer association broken down by the different polymorphisms analyzed.

Polymorphism Allele	Cases, *n* (%)	Controls, *n* (%)	OR[a] (95%CI)	p[c]	p-c[d]	OR[b] (95%CI)	p[c]	p-c[d]
ERCC5_rs1047768								
TC	220 (49.3)	312 (46.1)	1 (–)			1 (–)		
CC	150 (33.6)	229 (33.8)	0.94 (0.73–1.2)	0.6269	0.6697	0.98 (0.74–1.31)	0.9121	0.7469
TT	76 (17)	136 (20.1)	0.71 (0.52–0.96)	0.0271	0.1141	0.71 (0.49–1.01)	0.0583	0.1943
OGG1_Ser326Cys_rs1052133								
CC	391 (62.2)	577 (61)	1 (–)			1 (–)		
CG	209 (33.2)	307 (32.5)	0.92 (0.75–1.12)	0.4076	0.5687	0.99 (0.79–1.24)	0.9288	0.7503
GG	29 (4.6)	62 (6.6)	0.66 (0.43–1.01)	0.0598	0.1974	0.63 (0.39–1.02)	0.0638	0.2055
FATS_C10orf90_rs11245007								
CT	207 (46.4)	301 (44.4)	1 (–)			1 (–)		
CC	205 (46)	311 (45.9)	0.98 (0.78–1.24)	0.8933	0.7429	0.92 (0.70–1.21)	0.5505	0.6404
TT	34 (7.6)	66 (9.7)	1.01 (0.68–1.5)	0.9683	0.758	0.78 (0.48–1.25)	0.3116	0.502
APEX1_rs1130409								
GT	208 (46.6)	329 (48.5)	1 (–)			1 (–)		
TT	125 (28)	187 (27.6)	1.02 (0.78–1.33)	0.8805	0.7401	1.17 (0.86–1.6)	0.3074	0.4986
GG	113 (25.3)	162 (23.9)	1.03 (0.78–1.36)	0.8138	0.7247	1.14 (0.83–1.58)	0.4147	0.5729
ERCC1_rs11615								
CC	153 (24.2)	226 (23.9)	1 (–)			1 (–)		
CT	248 (39.3)	413 (43.6)	1.01 (0.79–1.28)	0.9469	0.7539	0.91 (0.69–1.2)	0.4948	0.6155
TT	230 (36.5)	308 (32.5)	1.25 (0.97–1.61)	0.0838	0.2435	1.16 (0.87–1.54)	0.3188	0.5077
OGG1_rs125701								
GG	328 (73.5)	497 (73.4)	1 (–)			1 (–)		
AG	103 (23.1)	165 (24.4)	0.89 (0.68–1.16)	0.3889	0.5571	0.93 (0.69–1.26)	0.6522	0.6784
AA	15 (3.4)	15 (2.2)	1.65 (0.84–3.28)	0.1466	0.3362	1.62 (0.73–3.57)	0.2321	0.4288
RRM1_rs12806698								
CC	248 (55.6)	388 (57.2)	1 (–)			1 (–)		
CA	170 (38.1)	252 (37.2)	0.99 (0.78–1.24)	0.9033	0.745	1.01 (0.77–1.32)	0.9587	0.7562
AA	28 (6.3)	38 (5.6)	0.97 (0.59–1.57)	0.8909	0.7424	1.08 (0.62–1.87)	0.7764	0.7152
ERCC2_Lys751Gln_rs13181								
TT	272 (43.1)	426 (45)	1 (–)			1 (–)		
GT	281 (44.5)	416 (43.9)	1.09 (0.9–1.33)	0.388	0.5565	1.05 (0.84–1.32)	0.6465	0.6765
GG	78 (12.4)	105 (11.1)	1.17 (0.87–1.57)	0.3074	0.4986	1.1 (0.78–1.55)	0.6004	0.6601
rs1452584								
AA	281 (63)	465 (68.6)	1 (–)			1 (–)		
GA	183 (30.9)	189 (27.9)	1.08 (0.85–1.38)	0.52	0.6271	1.17 (0.88–1.55)	0.2936	0.4871
GG	27 (6.1)	24 (3.5)	1.45 (0.85–2.48)	0.1687	0.3624	1.61 (0.87–2.98)	0.126	0.3089
ERCC2_Asp312Asn_rs1799793								
TT	265 (59.4)	419 (61.9)	1 (–)			1 (–)		
CT	157 (35.2)	224 (33.1)	1.15 (0.91–1.46)	0.2468	0.4439	1.2 (0.91–1.58)	0.1948	0.3897
CC	24 (5.4)	34 (5)	1.04 (0.63–1.69)	0.8741	0.7387	1.03 (0.57–1.86)	0.9137	0.7472
NBN_rs1805794								
CC	188 (42.2)	313 (46.2)	1 (–)			1 (–)		
GC	202 (45.3)	304 (44.8)	1.06 (0.83–1.34)	0.6549	0.6793	1.09 (0.83–1.43)	0.5338	0.6332
GG	56 (12.6)	61 (9)	1.78 (1.23–2.58)	0.0022	0.0152	1.78 (1.15–2.75)	0.0102	0.0578
OGG1_C7G_rs2072668								
CC	274 (61.4)	405 (59.9)	1 (–)			1 (–)		
CG	150 (33.6)	228 (33.7)	0.88 (0.69–1.11)	0.2811	0.4762	0.96 (0.73–1.26)	0.7614	0.7112
GG	22 (4.9)	43 (6.4)	0.71 (0.42–1.15)	0.1691	0.3628	0.69 (0.38–1.21)	0.2025	0.397
ERCC5_rs2094258								
CC	281 (63)	441 (65.1)	1 (–)			1 (–)		
CT	139 (31.2)	204 (30.1)	1.05 (0.83–1.34)	0.684	0.6887	1.09 (0.82–1.44)	0.5672	0.6472
TT	26 (5.8)	32 (4.7)	0.95 (0.56–1.59)	0.8535	0.7341	1.13 (0.62–2.02)	0.6896	0.6905
XPC_rs2228001								
GT	214 (48)	332 (49)	1 (–)			1 (–)		
TT	162 (36.3)	234 (34.6)	0.99 (0.77–1.26)	0.909	0.7462	1.08 (0.81–1.44)	0.5805	0.6525
GG	70 (15.7)	111 (16.4)	0.95 (0.68–1.31)	0.7516	0.7085	0.86 (0.59–1.24)	0.4135	0.5722
OGG1_rs2472037								
AG	202 (45.5)	317 (47.5)	1 (–)			1 (–)		
AA	175 (39.4)	262 (39.2)	0.93 (0.73–1.18)	0.5533	0.6415	0.98 (0.74–1.3)	0.8976	0.7438
GG	67 (15.1)	89 (13.3)	1.16 (0.83–1.61)	0.3835	0.5537	1.31 (0.88–1.95)	0.1742	0.3685
XRCC1_Gln399Arg_rs25487								
GG	285 (45.2)	416 (43.9)	1 (–)			1 (–)		
AG	260 (41.2)	418 (44.1)	0.94 (0.77–1.14)	0.5226	0.6283	0.92 (0.74–1.16)	0.4951	0.6156
AA	86 (13.6)	113 (11.9)	1.15 (0.86–1.55)	0.3487	0.5301	1.12 (0.8–1.56)	0.5084	0.6218

Table 2 (*Continued*)

Polymorphism Allele	Cases, *n* (%)	Controls, *n* (%)	OR[a] (95%CI)	p[c]	p-c[d]	OR[b] (95%CI)	p[c]	p-c[d]
APEX1_rs3136817								
TT	238 (53.4)	347 (51.2)	1 (–)			1 (–)		
CT	172 (38.6)	261 (38.5)	0.96 (0.76–1.22)	0.7614	0.7112	0.87 (0.66–1.14)	0.3021	0.4942
CC	36 (8.1)	70 (10.3)	0.73 (0.48–1.1)	0.1404	0.3284	0.75 (0.47–1.19)	0.229	0.4255
ERCC1_rs3212986								
GG	360 (57.1)	554 (58.5)	1 (–)			1 (–)		
GT	237 (37.6)	342 (36.1)	1.14 (0.94–1.39)	0.1867	0.3816	1.06 (0.85–1.33)	0.5942	0.6578
TT	34 (5.4)	51 (5.4)	1.06 (0.7–1.59)	0.7721	0.7141	1.1 (0.68–1.76)	0.7003	0.6937
MUTYH_rs3219489								
CC	243 (54.7)	351 (51.8)	1 (–)			1 (–)		
GC	163 (36.7)	281 (41.5)	0.92 (0.73–1.16)	0.4965	0.6163	0.85 (0.65–1.12)	0.2454	0.4425
GG	38 (8.6)	45 (6.6)	1.52 (0.98–2.35)	0.059	0.1958	1.41 (0.85–2.33)	0.1867	0.3816
ERCC3_rs3738948								
AA	268 (60.1)	406 (59.9)	1 (–)			1 (–)		
GA	150 (33.6)	242 (35.7)	0.92 (0.72–1.16)	0.4849	0.6107	1.04 (0.79–1.38)	0.7624	0.7115
GG	28 (6.3)	30 (4.4)	1.52 (0.93–2.49)	0.097	0.2654	1.42 (0.8–2.52)	0.2326	0.4293
ERCC3_XPB_rs4150459								
CC	406 (91)	604 (89.3)	1 (–)			1 (–)		
CT	39 (8.7)	69 (10.2)	0.96 (0.65–1.39)	0.8141	0.7248	0.77 (0.49–1.19)	0.2445	0.4416
TT	1 (0.2)	3 (0.4)	0.48 (0.02–3.78)	0.523	0.6285	0.45 (0.02–3.54)	0.4865	0.6114
KLH4_rs5922437								
GG	285 (63.9)	422 (62.3)	1 (–)			1 (–)		
AA	83 (18.6)	155 (22.9)	0.94 (0.71–1.24)	0.677	0.6865	0.88 (0.63–1.23)	0.4492	0.5923
GA	78 (17.5)	100 (14.8)	1.04 (0.72–1.51)	0.819	0.726	0.86 (0.57–1.29)	0.4693	0.6029
XRCC3_Thr241Met_rs861539								
CC	238 (37.8)	374 (39.5)	1 (–)			1 (–)		
TG	306 (48.6)	420 (44.4)	1.13 (0.93–1.39)	0.2284	0.4249	1.24 (0.98–1.56)	0.0687	0.2149
TT	86 (13.7)	152 (16.1)	0.91 (0.69–1.21)	0.5388	0.6354	0.89 (0.64–1.23)	0.497	0.6165

[a] Adjusted by age and sex.
[b] Adjusted by age, sex, tobacco consumption and indoor radon exposure.
[c] *p*-Values.
[d] Corrected *p*-values.

Table 3
Lung cancer association broken down by smoking status for the different polymorphisms analyzed.*

Polymorphisms	Cases, controls; OR[a] (95%CI)								
	Never-smokers	p[b]	p-c[c]	Moderate smokers	p[b]	p-c[c]	Heavy smokers	p[b]	p-c[c]
ERCC5_rs1047768									
TC	92, 136			34, 106			56, 51		
	1 (–)			0.79 (0.48–1.3)	0.3592	0.5374	2.82 (1.7–4.71)	0.0001	0.0012
CC	62, 113			32, 71			29, 34		
	0.87 (0.57–1.34)	0.525	0.6294	1.1 (0.65 –1.87)	0.7174	0.6988	2.1 (1.15–3.84)	0.0156	0.0789
TT	25, 57			9, 50			21, 18		
	0.58 (0.33–1.02)	0.0628	0.2035	0.45 (0.19–0.94)	0.0437	0.1604	2.64 (1.29–5.47)	0.0083	0.0491
OGG1_Ser326Cys_rs1052133									
CC	225, 353			41, 136			74, 60		
	1 (–)			0.7 (0.46–1.4)	0.0837	0.2433	2.82 (1.87–4.26)	<0.001	<0.001
CG	120, 183			30, 74			29, 38		
	0.98 (0.73–1.31)	0.876	0.7391	0.92 (0.56–1.47)	0.724	0.7008	1.77 (1.02 –3.03)	0.0387	0.1471
GG	18, 39			2, 16			3, 5		
	0.64 (0.35–1.15)	0.147	0.3367	0.28 (0.04–1.02)	0.0975	0.2661	1.36 (0.27–5.7)	0.6809	0.6877
FATS_C10orf90_rs11245007									
CT	85, 132			37, 110			45, 43		
	1 (–)			0.84 (0.51–1.37)	0.4955	0.6158	2.74 (1.6–4.74)	0.0003	0.0027
CC	80, 144			32, 92			54, 52		
	0.88 (0.58–1.32)	0.5222	0.6281	0.93 (0.55–1.57)	0.7944	0.7199	2.62 (1.58–4.4)	0.0002	0.002
TT	14, 30			6, 25			7, 8		
	0.76 (0.36–1.54)	0.4158	0.5937	0.6 (0.21–1.48)	0.294	0.4874	2.27 (0.75–6.73)	0.1357	0.3222
APEX1_rs1130409									
GT	121, 176			6, 33			15, 11		
	1 (–)			0.39 (0.14–0.92)	0.2777	0.4732	3.32 (1.44–7.87)	0.0000	0.0027
TT	139, 233			32, 110			41, 52		
	0.91 (0.66–1.26)	0.5152	0.625	0.68 (0.41–1.1)	0.724	0.7008	1.82 (1.09–3.03)	0.017	0.0836
GG	103, 166			37, 84			50, 40		
	1.05 (0.74–1.48)	0.1551	0.3465	1.02 (0.62–1.64)	0.6638	0.6822	2.81 (1.7–4.7)	<0.001	<0.001

Table 3 (*Continued*)

Polymorphisms	Cases, controls; OR[a] (95%CI)								
	Never-smokers	p[b]	p-c[c]	Moderate smokers	p[b]	p-c[c]	Heavy smokers	p[b]	p-c[c]
ERCC1_rs11615									
CC	121, 176			6, 33			15, 11		
	1 (–)			0.39 (0.14–0.92)	0.0459	0.1659	3.32 (1.44–7.87)	0.0051	0.0326
CT	139, 233			32, 110			41, 52		
	0.91 (0.66–1.26)	0.5835	0.6537	0.68 (0.41–1.1)	0.1206	0.3011	1.82 (1.09–3.03)	0.0205	0.0952
TT	103, 166			37, 84			50, 40		
	1.05 (0.74–1.48)	0.8032	0.7221	1.02 (0.62–1.64)	0.9504	0.745	2.81 (1.7–4.7)	0.0001	0.0012
OGG1_rs125701									
GG	129, 215			60, 172			73, 76		
	1 (–)			0.99 (0.66–1.49)	0.9734	0.7589	2.64 (1.72–4.09)	<0.001	<0.001
AG	44, 82			13, 50			28, 25		
	0.91 (0.58–1.42)	0.6749	0.6858	0.65 (0.32–1.24)	0.2071	0.4013	3.11 (1.67–5.81)	0.0003	0.0027
AA	6, 9			2, 4			5, 2		
	1.13 (0.35–3.44)	0.8349	0.7298	1.47 (0.2–7.77)	0.663	0.682	8.04 (1.64–58.29)	0.0158	0.0796
RRM1_rs12806698									
CC	103, 162			44, 145			57, 59		
	1 (–)			0.78 (0.5–1.23)	0.2938	0.4873	2.46 (1.51–4.01)	0.003	0.0027
CA	64, 124			28, 73			41, 37		
	0.81 (0.53–1.22)	0.319	0.5078	1 (0.58–1.69)	0.9928	0.7625	2.91 (1.67–5.11)	0.0002	0.002
AA	12, 20			3, 9			8, 7		
	1.01 (0.45–2.21)	0.9741	0.7591	0.82 (0.18–2.93)	0.7807	0.7163	2.99 (1.02–9.01)	0.0453	0.1644
ERCC2_Lys751Gln_rs13181									
TT	157, 263			33, 103			50, 37		
	1 (–)			0.84 (0.52–1.34)	0.4737	0.6051	3.55 (2.16–5.9)	0.0000	0.0000
GT	165, 242			33, 104			42, 54		
	1.18 (0.89–1.57)	0.2502	0.4473	0.77 (0.48–1.21)	0.2638	0.4604	1.94 (1.2–3.13)	0.007	0.0427
GG	41, 70			9, 20			14, 12		
	0.94 (0.61–1.49)	0.8562	0.7347	1.2 (0.5–2.68)	0.6745	0.6857	2.89 (1.27–6.68)	0.0113	0.0625
rs1452584									
AA	106, 217			45, 149			72, 74		
	1 (–)			0.99 (0.63–1.53)	0.9601	0.7564	3.06 (1.97–4.78)	<0.001	<0.001
GA	61, 81			25, 68			31, 25		
	1.38 (0.9–2.12)	0.1367	0.3235	1.13 (0.65–1.92)	0.6691	0.684	3.88 (2.11–7.22)	<0.001	<0.001
GG	12, 8			5, 10			3, 4		
	2.36 (0.91–6.42)	0.0794	0.2356	1.29 (0.38–3.92)	0.6656	0.6828	2.49 (0.47–11.89)	0.2484	0.4455
ERCC2_Asp312Asn_rs1799793									
TT	119, 193			41, 132			62, 61		
	1 (–)			0.83 (0.52–1.29)	0.4088	0.5694	2.68 (1.68–4.28)	<0.001	<0.001
CT	53, 94			32, 87			36, 35		
	0.97 (0.63–1.49)	0.8854	0.7412	1.03 (0.62–1.68)	0.9225	0.749	2.9 (1.65–5.1)	0.0002	0.002
CC	7, 19			2, 8			8, 6		
	0.62 (0.23–1.54)	0.3232	0.5111	0.64 (0.09–2.75)	0.5925	0.6571	3.64 (1.18–11.81)	0.0249	0.1082
NBN_rs1805794									
CC	74, 144			35, 106			38, 44		
	1 (–)			1.05 (0.63–1.74)	0.8462	0.7324	2.87 (1.64–5.05)	0.0002	0.002
GC	76, 135			31, 99			57, 48		
	1.07 (0.7–1.62)	0.7615	0.7112	1.12 (0.66–1.91)	0.6693	0.684	4.04 (2.39–6.88)	<0.001	<0.001
GG	29, 27			9, 22			11, 11		
	2.72 (1.44–5.2)	0.0022	0.0152	1.21 (0.49–2.78)	0.6632	0.6821	3.04 (1.21–7.69)	0.0172	0.0843
OGG1_C7G_rs2072668									
CC	106, 181			43, 137			74, 60		
	1 (–)			0.87 (0.55–1.37)	0.5564	0.6428	3.41 (2.16–5.44)	<0.001	<0.001
CG	63, 105			29, 73			29, 38		
	0.97 (0.64–1.47)	0.8773	0.7394	1.06 (0.62–1.78)	0.8262	0.7277	2.03 (1.13–3.63)	0.0175	0.0852
GG	10, 20			3, 16			3, 5		
	0.74 (0.31–1.67)	0.4833	0.6099	0.49 (0.11–1.56)	0.2759	0.4716	1.45 (0.28–6.24)	0.6254	0.6692
ERCC5_rs2094258									
CC	118, 198			47, 144			64, 68		
	1 (–)			0.88 (0.57–1.35)	0.5622	0.6452	2.42 (1.54–3.82)	0.0001	0.0012
CT	53, 98			25, 69			35, 28		
	0.83 (0.54–1.27)	0.3909	0.5584	0.97 (0.56–1.65)	0.9041	0.7452	3.63 (2.02 –6.59)	<0.001	<0.001
TT	8, 10			3, 14			7, 7		
	1.12 (0.4–3.14)	0.8216	0.7266	0.51 (0.11–1.66)	0.3067	0.498	2.42 (0.77–7.56)	0.1218	0.3028
XPC_rs2228001									
GT	86, 164			36, 106			51, 48		
	1 (–)			1.02 (0.62–1.65)	0.9511	0.7547	3.29 (1.97–5.53)	<0.001	<0.001
TT	65, 108			27, 82			37, 25		
	1.16 (0.76–1.77)	0.4977	0.6168	1.08 (0.62–1.84)	0.7911	0.719	4.78 (2.6–8.92)	<0.001	<0.001
GG	28, 34			12, 39			18, 30		
	1.45 (0.79–2.63)	0.2258	0.4221	0.96 (0.45–1.95)	0.9217	0.7488	1.8 (0.9–3.52)	0.0904	0.2548

Table 3 (*Continued*)

Polymorphisms	Cases, controls; OR[a] (95%CI)								
	Never-smokers	p[b]	p-c[c]	Moderate smokers	p[b]	p-c[c]	Heavy smokers	p[b]	p-c[c]
OGG1_rs2472037									
AG	73, 140			38, 105			54, 55		
	1 (–)			1.17 (0.7–1.93)	0.5496	0.64	3.11 (1.86–5.24)	<0.001	<0.001
AA	75, 121			25, 84			39, 41		
	1.15 (0.75–1.77)	0.5187	0.6266	0.91 (0.51–1.58)	0.7425	0.706	2.98 (1.69–5.28)	0.0002	0.002
GG	30, 38			11, 36			13, 7		
	1.73 (0.96–3.13)	0.0678	0.2132	1.04 (0.47–2.18)	0.9197	0.7484	6.1 (2.3–17.5)	0.0004	0.0034
XRCC1_Gln399Arg_rs25487									
GG	169, 257			32, 94			45, 45		
	1 (–)			0.78 (0.48–1.24)	0.2954	0.4886	2.28 (1.4–3.7)	0.0009	0.007
AG	145, 247			36, 108			43, 45		
	0.89 (0.67–1.19)	0.4299	0.5817	0.74 (0.47–1.16)	0.1984	0.3932	2.16 (1.32–3.53)	0.0022	0.0152
AA	49, 71			7, 25			18, 13		
	1.08 (0.71–1.64)	0.7276	0.7018	0.64 (0.25–1.48)	0.3272	0.5142	3.19 (1.49–7.01)	0.003	0.0203
APEX1_rs3136817									
TT	104, 151			42, 123			54, 57		
	1 (–)			0.81 (0.51–1.29)	0.3818	0.5526	2.36 (1.44–3.88)	0.0007	0.0056
CT	63, 121			26, 81			45, 35		
	0.76 (0.5–1.15)	0.1921	0.387	0.76 (0.44–1.29)	0.3224	0.5105	2.98 (1.73– 5.19)	0.0001	0.0012
CC	12, 34			7, 23			7, 11		
	0.54 (0.25–1.1)	0.0981	0.2671	0.76 (0.29–1.83)	0.564	0.6459	1.33 (0.46– 3.62)	0.5763	0.6508
ERCC1_rs3212986									
GG	194, 339			49, 132			62, 58		
	1 (–)			0.98 (0.65–1.45)	0.9071	0.7458	2.81 (1.82–4.35)	<0.001	<0.001
GT	146, 202			25, 82			37, 42		
	1.27 (0.95–1.68)	0.1029	0.2743	0.79 (0.47–1.29)	0.3562	0.5353	2.31 (1.38–3.84)	0.0013	0.0097
TT	23, 34			1, 13			7, 3		
	1.25 (0.7–2.2)	0.4423	0.5886	0.2 (0.01–1.01)	0.1188	0.2984	5.92 (1.59–28.18)	0.0118	0.0646
MUTYH_rs3219489									
CC	91, 157			35, 118			72, 55		
	1 (–)			0.83 (0.5–1.34)	0.445	0.5901	3.69 (2.29–6.01)	<0.001	<0.001
GC	72, 126			31, 94			28, 42		
	0.95 (0.63–1.43)	0.7974	0.7206	0.91 (0.54–1.51)	0.7201	0.6996	1.93 (1.07–3.46)	0.0281	0.1166
GG	16, 23			9, 15			6, 6		
	1.27 (0.61–2.62)	0.52	0.6271	1.93 (0.75–4.74)	0.1584	0.3505	2.16 (0.64–7.3)	0.2028	0.3973
ERCC3_rs3738948									
AA	112, 173			46, 139			59, 62		
	1 (–)			0.84 (0.54–1.3)	0.4379	0.5862	2.33 (1.46–3.74)	0.0004	0.0034
GA	57, 119			24, 79			39, 35		
	0.79 (0.52–1.2)	0.2791	0.4744	0.83 (0.47–1.43)	0.5078	0.6216	3.17 (1.81–5.58)	0.0001	0.0012
GG	10, 14			5, 9			8, 6		
	1.1 (0.44–2.65)	0.8375	0.7304	1.36 (0.4–4.17)	0.5948	0.658	3.5 (1.15–11.22)	0.0281	0.1166
ERCC3_XPB_rs4150459									
CC	162, 269			69, 202			98, 95		
	1 (–)			0.39 (0.13–0.99)	0.0684	0.2143	2.34 (0.82–6.72)	0.1082	0.282
CT	17, 33			5, 24			8, 8		
	0.94 (0.48–1.78)	0.8539	0.7342	1.32 (0.05–33.83)	0.8467	0.7325	2.59 (1.89–3.55)	<0.001	<0.001
TT	0, 2			1, 1			0, 0		
	–			2.9 (1.96–4.33)	<0.001	<0.001	–		
KLH4_rs5922437									
GG	101, 172			49, 145			72, 74		
	1 (–)			0.88 (0.56–1.36)	0.5582	0.6436	2.59 (1.64–4.11)	<0.001	<0.001
AA	26, 62			10, 62			27, 22		
	0.87 (0.5–1.5)	0.624	0.6687	0.48 (0.22–0.97)	0.0513	0.1788	3.02 (1.57–5.88)	0.001	0.0076
GA	52, 72			16, 20			7, 7		
	0.73 (0.45–1.17)	0.1964	0.3912	1.34 (0.63–2.79)	0.439	0.5868	1.53 (0.49– 4.76)	0.4541	0.5949
XRCC3_Thr241Met_rs861539									
CC	142, 241			19, 87			41, 34		
	1 (–)			0.55 (0.31–0.94)	0.0355	0.1381	3.05 (1.81–5.2)	<0.001	<0.001
TG	178, 243			43, 103			51, 53		
	1.32 (0.99–1.76)	0.0618	0.2015	1.12 (0.72–1.74)	0.6028	0.661	2.57 (1.61– 4.13)	0.0001	0.0012
TT	43, 91			12, 37			14, 16		
	0.8 (0.52–1.22)	0.3042	0496	0.86 (0.41–1.69)	0.6658	0.6829	2.41 (1.1–5.22)	0.0258	0.1106

[*] The reference category for each gene analyzed is having the wild type and being never-smoker.
[a] Adjusted by age, sex and indoor radon exposure.
[b] *p*-Values.
[c] Corrected *p*-values.

Table 4
Lung cancer association broken down by radon exposure for the different polymorphisms analyzed.*

Polymorphisms	Cases, controls; OR[a] (95%CI)					
	Indoor radon exposure (Bq/m3)					
	≤200	p[b]	p-c[c]	>200	p[b]	p-c[c]
ERCC5_rs1047768						
TC	131, 208			89, 104		
	1 (–)			1.39 (0.94–2.04)	0.0972	0.2657
CC	86, 146			64, 83		
	0.98 (0.68–1.41)	0.9136	0.7472	1.34 (0.88–2.05)	0.1737	0.3679
TT	51, 86			25, 50		
	0.87 (0.55–1.34)	0.5236	0.6288	0.66 (0.37–1.16)	0.1506	0.3411
OGG1_Ser326Cys_rs1052133						
CC	231, 374			160, 203		
	1 (–)			1.27 (0.97–1.68)	0.0843	0.2444
CG	117, 211			92, 96		
	0.87 (0.65–1.17)	0.3637	0.5405	1.53 (1.09–2.16)	0.0145	0.075
GG	18, 42			11, 20		
	0.64 (0.35–1.15)	0.146	0.3355	0.78 (0.34–1.69)	0.5404	0.6361
FATS_C10orf90_rs11245007						
CT	134, 198			73, 103		
	1 (–)			1.03 (0.69–1.53)	0.8875	0.7416
CC	118, 202			87, 109		
	0.82 (0.59–1.15)	0.2559	0.4529	1.14 (0.77–1.67)	0.515	0.6249
TT	16, 41			18, 25		
	0.57 (0.29–1.08)	0.092	0.2574	1.22 (0.6–2.43)	0.5814	0.6528
APEX1_rs1130409						
GT	135, 206			73, 123		
	1 (–)			1 (0.68–1.47)	0.7598	0.7638
TT	71, 125			54, 62		
	1.06 (0.71–1.56)	0.7868	0.7179	1.4 (0.89–2.22)	0.1458	0.3352
GG	62, 110			51, 52		
	0.94 (0.63–1.42)	0.7834	0.717	1.68 (1.04–2.73)	0.0341	0.1341
ERCC1_rs11615						
CC	90, 159			63, 67		
	1 (–)			1.73 (1.1–2.59)	0.0155	0.0785
CT	137, 261			111, 152		
	0.97 (0.69–1.38)	0.8823	0.7405	1.34 (0.92–1.94)	0.1257	0.3085
TT	140, 208			90, 100		
	1.24 (0.87–1.77)	0.2274	0.4238	1.65 (1.1–2.48)	0.0158	0.0796
OGG1_rs125701						
GG	194, 331			134, 166		
	1 (–)			1.42 (1.04–1.94)	0.0294	0.1198
AG	68, 101			35, 64		
	1.1 (0.75–1.6)	0.6224	0.6681	0.95 (0.59–1.53)	0.8417	0.7314
AA	6, 8			9, 7		
	2.03 (0.63–6.25)	0.2185	0.4141	1.73 (0.6–5.12)	0.3085	0.4995
RRM1_rs12806698						
CC	156, 245			92, 143		
	1 (–)			1.05 (0.74–1.5)	0.7816	0.7166
CA	97, 174			73, 78		
	0.87 (0.61–1.22)	0.4099	0.57	1.42 (0.94–2.14)	0.0934	0.257
AA	15, 22			13, 16		
	1.02 (0.48–2.1)	0.9553	0.7555	1.24 (0.55–2.77)	0.6022	0.6608
ERCC2_Lys751Gln_rs13181						
TT	158, 283			114, 143		
	1 (–)			1.4 (1.01–1.94)	0.0428	0.1581
GT	160, 275			121, 141		
	1.02 (0.77–1.36)	0.8886	0.7419	1.56 (1.13–2.15)	0.0074	0.0447
GG	49, 70			29, 35		
	1.18 (0.77–1.81)	0.4376	0.586	1.35 (0.77–2.35)	0.2909	0.4848
rs1452584						
AA	162, 298			119, 167		
	1 (–)			1.27 (0.91–1.75)	0.1543	0.3456
GA	92, 127			46, 62		
	1.23 (0.86–1.75)	0.2559	0.4529	1.35 (0.85–2.13)	0.2007	0.3954
GG	14, 16			13, 8		
	1.19 (0.54–2.6)	0.6604	0.6811	3.04 (1.15–8.48)	0.0273	0.1146

Table 4 (*Continued*)

Polymorphisms	Cases, controls; OR[a] (95%CI)					
	Indoor radon exposure (Bq/m3)					
	≤200	p[b]	p-c[c]	>200	p[b]	p-c[c]
ERCC2_Asp312Asn_rs1799793						
TT	153, 280			112, 139		
	1 (–)			1.52 (1.08–2.14)	0.0162	0.0809
CT	101, 137			56, 87		
	1.47 (1.04–2.9)	0.0295	0.1201	1.31 (0.86–2.01)	0.2065	0.4008
CC	14, 23			10, 11		
	1.2 (0.56–2.51)	0.6323	0.6716	1.32 (0.51–3.38)	0.5595	0.6441
NBN_rs1805794						
CC	112, 202			76, 111		
	1 (–)			1.12 (0.75–1.68)	0.565	0.6463
GC	121, 199			81, 105		
	0.98 (0.69–1.39)	0.9223	0.7489	1.46 (0.98–2.18)	0.0658	0.2094
GG	35, 40			21, 21		
	1.88 (1.09–3.24)	0.0231	0.1031	1.91 (0.94–3.88)	0.0724	0.2223
OGG1_C7G_rs2072668						
CC	165, 258			109, 147		
	1 (–)			1.18 (0.84–1.65)	0.3477	0.5293
CG	88, 153			62, 75		
	0.88 (0.62–1.25)	0.4729	0.6047	1.28 (0.84–1.94)	0.25	0.4471
GG	15, 28			7, 15		
	0.76 (0.38–1.51)	0.4483	0.5918	0.63 (0.22–1.66)	0.3646	0.5411
ERCC5_rs2094258						
CC	164, 284			117, 157		
	1 (–)			1.32 (0.95–1.84)	0.1021	0.2732
CT	84, 131			55, 73		
	1.15 (0.8–1.64)	0.4523	0.594	1.32 (0.86–2.03)	0.2034	0.3979
TT	20, 25			6, 7		
	1.18 (0.6–2.28)	0.6264	0.6695	1.16 (0.34–3.9)	0.8081	0.7233
XPC_rs2228001						
GT	135, 217			79, 115		
	1 (–)			1.15 (0.78–1.69)	0.4692	0.6028
TT	99, 154			63, 80		
	1.04 (0.73–1.49)	0.8162	0.7253	1.31 (0.86–2)	0.2132	0.4081
GG	34, 70			36, 41		
	0.72 (0.43–1.18)	0.1989	0.3936	1.25 (0.73–2.13)	0.4123	0.5715
OGG1_rs2472037						
AG	114, 211			88, 106		
	1 (–)			1.5 (1.01–2.22)	0.0438	0.1606
AA	109, 165			66, 97		
	1.14 (0.8–1.62)	0.483	0.6097	1.15 (0.76–1.74)	0.5008	0.6183
GG	44, 56			23, 33		
	1.44 (0.88–2.34)	0.1471	0.3368	1.64 (0.86–3.07)	0.126	0.3089
XRCC1_Gln399Arg_rs25487						
GG	165, 276			120, 140		
	1 (–)			1.36 (0.98–1.88)	0.0622	0.2023
AG	151, 272			109, 146		
	0.91 (0.68–1.21)	0.5177	0.6261	1.31 (0.95–1.82)	0.1041	0.2761
AA	51, 80			35, 33		
	1.07 (0.7–1.61)	0.7657	0.7124	1.7 (1–2.91)	0.0499	0.1756
APEX1_rs3136817						
TT	139, 232			99, 115		
	1 (–)			1.35 (0.94–1.95)	0.1062	0.2792
CT	107, 158			65, 103		
	0.97 (0.68–1.33)	0.8541	0.7342	1 (0.66–1.49)	0.9874	0.7616
CC	22, 51			14, 19		
	0.69 (0.38–1.21)	0.2077	0.4018	1.27 (0.57–2.78)	0.5455	0.6383
ERCC1_rs3212986						
GG	208, 373			152, 181		
	1 (–)			1.5 (1.12–1.99)	0.0057	0.0359
GT	139, 219			98, 123		
	1.15 (0.86–1.52)	0.3395	0.5234	1.47 (1.06–2.04)	0.0214	0.098
TT	20, 36			14, 15		
	1.08 (0.59–1.94)	0.7928	0.7194	1.77 (0.8–3.88)	0.1503	0.3408

Table 4 (*Continued*)

Polymorphisms	Cases, controls; OR[a] (95%CI)					
	Indoor radon exposure (Bq/m3)					
	≤200	p[b]	p-c[c]	>200	p[b]	p-c[c]
MUTYH_rs3219489						
CC	141, 230			102, 121		
	1 (–)			1.37 (0.95–1.98)	0.0873	0.2496
GC	100, 176			63, 105		
	0.91 (0.64–1.28)	0.5925	0.6571	1.08 (0.72–1.61)	0.7206	0.6998
GG	26, 35			12, 10		
	1.49 (0.82–2.67)	0.1873	0.3822	1.68 (0.65–4.39)	0.2838	0.4786
ERCC3_rs3738948						
AA	160, 262			108, 144		
	1 (–)			1.19 (0.84–1.67)	0.3193	0.5081
GA	92, 159			58, 83		
	0.97 (0.69–1.37)	0.872	0.7383	1.29 (0.84–1.96)	0.2395	0.4365
GG	16, 20			12, 10		
	1.28 (0.61–2.62)	0.5096	0.6224	2 (0.79–5.18)	0.1441	0.3331
ERCC3_XPB_rs4150459						
CC	244, 399			162, 205		
	1 (–)			1.29 (0.97–1.71)	0.0762	0.2296
CT	24, 38			15, 31		
	0.92 (0.51–1.61)	0.7645	0.712	0.83 (0.41–1.59)	0.5796	0.6521
TT	0, 2			1, 1		
	–			1.69 (0.07–43.58)	0.714	0.6978
KLH4_rs5922437						
GG	170, 287			115, 135		
	1 (–)			1.5 (1.07–2.1)	0.019	0.0903
AA	47, 96			36, 59		
	0.96 (0.62–1.46)	0.8355	0.7299	1.14 (0.69–1.88)	0.5947	0.658
GA	51, 57			27, 43		
	1.16 (0.72–1.89)	0.5392	0.6356	0.82 (0.46–1.45)	0.4993	0.6176
XRCC3_Thr241Met_rs861539						
CC	132, 238			106, 136		
	1 (–)			1.41 (1–1.99)	0.052	0.1804
TG	181, 283			125, 137		
	1.21 (0.9–1.63)	0.1983	0.3931	1.79 (1.28–2.51)	0.0008	0.0063
TT	54, 107			32, 45		
	0.92 (0.61–1.37)	0.6708	0.6845	1.2 (0.71–2.02)	0.4967	0.6164

[*] The reference category for each gene analyzed is having the wild type and being exposed to a radon concentration < 200 Bq/m^3.

[a] Adjusted by age, sex and tobacco consumption.

[b] *p*-Values.

[c] Corrected *p*-values.

important amount of never-smokers from the LCRINS study (Lung Cancer Association in Never Smokers), where this histological type is the most frequent. Nevertheless, this fact favoured that we had the same percentage of cases of each sex (50% each), allowing for a better interpretation of the results both for men and women.

This study has also a number of advantages. First, the sample size is relatively large, and we have been able to include information regarding the second association factor of lung cancer, which is indoor radon exposure. This is of particular importance because there is a lack of information on the mechanisms of radon causing lung cancer. It is important to note that Galicia is a radon prone-area[32,33] and the median time that cases and controls have been living at the same residence is high enough to induce lung cancer. Finally, the high participation rate and the multicentric nature of this research increase the external validity of its results.

In conclusion, these findings support that polymorphisms located in BER and NER pathways do not have an association with lung cancer onset, with the exception of the gene NBN (rs1805794). Nevertheless, this study support the hypothesis of their role modulating the effect of tobacco consumption, where heavy smokers might have their lung cancer association modulated by polymorphisms located in the BER and NER pathways. This could also happen for those individuals having high indoor radon exposures though at a minor extent.

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Conflict of interests

Dr. Kelsey is a founder and scientific advisor for Cellintec, which had no role in this research.

The authors declare no conflict of interests.

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