Indoor Radon in *EGFR*- and *BRAF*-Mutated and *ALK*-Rearranged Non–Small-Cell Lung Cancer Patients

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Abstract

Radon is the first cause of lung cancer in nonsmokers according to the World Health Organization (WHO), which recommends not exceeding 100Bq/m^3 in homes. No risk factor has yet been identified for non–small-cell lung cancer (NSCLC) harboring driver alterations, mainly nonsmokers. We found a median concentration of 104 Bq/m^3, above the WHO recommendation in *EGFR*-mutated, *BRAF*-mutated, and *ALK*-rearranged NSCLC patients, with no differences between them.

Background: Radon gas is the leading cause of lung cancer in the nonsmoking population. The World Health Organization (WHO) recommends indoor concentrations of < 100 Bq/m^3. Several molecular alterations have been described in non–small-cell lung cancer (NSCLC), mainly in nonsmokers, with no risk factors identified. We studied the role of indoor radon in NSCLC patients harboring specific driver alterations. **Patients and Methods:** We assessed the radon concentration from *EGFR*-, *BRAF*-mutated (m), and *ALK*-rearranged (r) NSCLC patients measured by an alpha-track detector placed in their homes between September 2014 and August 2015. Clinical characteristics were collected prospectively, and pathologic samples were reviewed retrospectively. **Results:** Forty-eight patients were included (36 *EGFRm*, 10 *ALKr*, 2 *BRAFm*). Median radon concentration was 104 Bq/m^3 (IQR 69-160) overall, and was 96 Bq/m^3 (42-915) for *EGFRm*, 116 (64-852) for *ALKr*, and 125 for *BRAFm*, with no significant differences. Twenty-seven patients (56%) had indoor radon above WHO recommendations, 8 (80%) of 10 *ALKr*, 2 (100%) of 2 *BRAFm*, and 17 (47%) of 36 *EGFRm*. **Conclusion:** The median indoor radon concentration was above the WHO recommendations, with no differences between *EGFR*, *ALK*, and *BRAF* patients. Concentrations above the WHO recommendations were most common with *ALKr* and *BRAFm*. These findings should be validated in larger studies.

Clinical Lung Cancer, Vol. 20, No. 4, 305-12
Keywords: Driver oncogene, Radioactivity, Radon gas, NSCLC

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Submitted: Dec 27, 2018; Revised: Mar 26, 2019; Accepted: Apr 16, 2019; Epub: May 3, 2019

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1525-7304/$ - see frontmatter
https://doi.org/10.1016/j.cllc.2019.04.009

Introduction

Radon Gas and Lung Cancer

Lung cancer is a major health problem, representing the main cause of cancer death worldwide.[1] Radon is considered the second most common cause of lung cancer after smoking, and the first in the nonsmoking population.[2,3] The International Agency for Research on Cancer recognizes radon gas as a human carcinogen group A, alongside tobacco and its derivatives. Indoor radon exposure comprises the largest source of natural radiation (50%) for humans, and radon-222 and its short-line descendants (polonium-218, lead-214, bismuth-214) derive from the uranium chain decay. It is an odorless, colorless, and tasteless radioactive gas, and its indoor concentration is closely related with the uranium content of rocks on the earth's crust beneath dwellings.

In 2003, Pavia et al[4] published the first meta-analysis on the association of indoor radon and lung cancer, comprising 17 case–control studies, one of which was performed in a Spanish population, showing a 24% increased risk of lung cancer in patients exposed to more than 150 Bq/m^3, with an odds ratio of 1.24 (95% confidence interval [CI], 1.11-1.38). The most cited study to date is a pooled analysis from 13 European case–control studies, which showed a linear and statistically significant increase of 16% (95% CI, 5% to 31%) of lung cancer risk per 100 Bq/m^3 of indoor radon.[5]

Europe has several radon-prone areas, notably the granite areas of the Iberian Peninsula, the Massif Central in France, and the Bohemian Massif in central Europe. More than 30% of the surface area of the countries participating in the European Indoor Radon Map, including Spain, has a median concentration above 100 Bq/m^3, and 4.2% is above 300 Bq/m^3.[6]

Unfortunately, indoor radon exposure is not consistently regulated in European countries.[7] The World Health Organization (WHO) recommends radon concentrations of < 100 Bq/m^3 (or 300 Bq/m^3 in cases where 100 Bq/m^3 cannot be achieved),[2] and the European Commission for Atomic Energy has established a nonregulatory recommendation (2013/59/Euratom) to not exceed 300 Bq/m^3 in European homes.[6] In contrast, the US Environmental Protection Agency establishes two levels of risk, one for the general population > 74 Bq/m^3 (> 2 pCi/L), when an action against radon is "recommended," and $> 148 Bq/m^3$ (> 4 pCi/L), when an action against radon is "necessary."[8]

In 2014, the Spanish Nuclear Safety Council reported the Spanish Indoor Radon map, classifying the country into 3 risk zones: low ($< 150 Bq/m^3$), medium (150-200Bq/m^3), and high ($> 200 Bq/m^3$), with a median value of 80.3Bq/m^3.[9,10]

Radon Gas and Molecular Alterations in Non–Small-Cell Lung Cancer

A thorough understanding of the carcinogenic mechanism behind radon and lung cancer, along with consequences, is lacking. Radon emits ionizing radiation type alpha (high-energy transfer capacity), which has been linked to a wide variety of cytotoxic and genotoxic effects in preclinical studies, which could favor carcinogenesis.[11-13] When alpha particles are inhaled, they affect the respiratory epithelium, causing DNA damage within these cells. A wide variety of molecular alterations has been associated with the radioactive alpha particles (mutations as point deletions or substitutions, chromosomal abnormalities as rearrangements, high instability, etc), and have generally been studied in peripheral blood lymphocytes of the radon-exposed population.[12,13] No clear association has been observed with TP53 alterations and radon exposure.[14]

Over recent years, several oncogenic molecular alterations have been described in non–small-cell lung cancer (NSCLC) patients, particularly adenocarcinoma. Typically somatic mutations (eg, *EGFR, BRAF*) or chromosomal rearrangements (*ALK* or *ROS1*) act as drivers for lung cancer, mainly in the nonsmoking population, although no risk factors have yet been specifically associated with them.

Indoor Radon and Clinical Characteristics

Radon has been associated with a wide range of different lung cancer histologies; it is the most common subtype of adenocarcinoma in never-smoker lung cancer patients.[5,15] To date, there is a lack of information about the clinical characteristics of radon-related lung cancer.

We hypothesized that the damage induced by radon gas and/or its short-line descendants may be related to these molecular alterations. To date, two studies have evaluated the role of indoor radon and molecular alteration in NSCLC. Taga et al[16] in 2012 reported no association between indoor radon and *EGFR* mutations in a prospective nonsmoker cohort of women ($n = 24$); and Ruano-Raviña et al[17] showed nonsignificant higher radon concentrations for *ALK*-positive ($n = 12$) versus -negative patients ($n = 80$), with a trend toward significance for higher concentrations in *EGFR* exon 19 deletion ($n = 49$) versus exon 21 (L858R) ($n = 34$) in a case series of never smokers from a multicenter study.

The aim of this study was to assess the relation between indoor radon concentrations and molecular alterations in a prospective Spanish cohort of *EGFR*- or *BRAF*-mutated (m) and *ALK*-rearranged (r) NSCLC patients. In addition, we evaluated the relation between indoor radon concentrations, and the clinical and pathologic features of these populations.

Patients and Methods

Study Population and Design

A prospective observational study assessing the relation between indoor radon concentration and selected driver molecular alterations was performed in NSCLC patients. All consecutive NSCLC patients harboring *EGFRm*, *BRAFm*, and *ALKr* treated in the Oncology Department at Ramón y Cajal University Hospital (Madrid, Spain) were invited to participate. After written informed consent was provided, all subjects were prospectively enrolled between September 2014 and August 2015. The research was conducted according to the principles of the Declaration of Helsinki, and the local institutional review committee approved the study procedures.

Inclusion Criteria

To be eligible, patients had to be 18 years or older, have a pathologically confirmed diagnosis of NSCLC with *EGFRm*, *BRAFm*, *ALKr*, or *ROS1r*, and have an estimated life expectancy of at least 3 months.

Table 1 Baseline Characteristics According to Molecular Subgroup

Characteristic	*EGFRm* (N = 36)	*ALKr* (N = 10)	*BRAFm* (N = 2)	Overall (N = 48)	*P*
Sex					NS
Male	11 (31)	4 (40)	0	15 (31)	
Female	25 (69)	6 (60)	2 (100)	33 (69)	
Age					.013[a]
Median (range) (y)	68 (47-82)	53 (29-69)	67 (57-77)	66.5 (29-82)	
<50 y	3 (8)	3 (30)	0	6 (13)	
50-70 y	19 (53)	7 (70)	1 (50)	27 (56)	
>70 y	14 (39)	0	1 (50)	15 (31)	
Smoking Status					NS
Never smoker	22 (61)	9 (90)	2 (100)	33 (69)	
Light smoker[b]	2 (6)	1 (10)	0	3 (6)	
Smoker	14 (39)	1 (10)	0	15 (31)	
ETS[c]					NS
No	12 (54.5)	4 (44)	2 (100)	18 (54.5)	
Yes	10 (45.5)	5 (56)	0	15 (45.5)	
Adenocarcinoma histology	36 (100)	10 (100)	2 (100)	48 (100)	—
Stage at diagnosis					NS
I-II	10 (28)	1 (10)	1 (50)	12 (25)	
IIIA	3 (8)	1 (10)	0	4 (8)	
IIIB-IV	23 (64)	8 (80)	1 (50)	32 (67)	

Data are presented as n (%) unless otherwise indicated.
Abbreviations: *ALKr* = *ALK* rearranged; *BRAFm* = *BRAF* mutated; *EGFRm* = *EGFR* mutated; ETS = environmental tobacco exposure; NS = not significant.
[a]Kruskal-Wallis test.
[b]Light smoker defined as < 15 pack-years.
[c]Only if never smokers.

Methods

Molecular Analysis. Molecular analysis was performed according to the routine practice of the pathology department of the Ramón y Cajal University Hospital. *EGFRm* and *BRAFm* were analyzed by quantitative real-time PCR (Cobas; Roche), and *ALKr* or *ROS1r* by fluorescence in-situ hybridization [Vysis LSI ALK Break Apart Rearrangement; Vysis LSI ROS1 (cen) SpectrumGreen or ROS1 (tel) SpectrumOrange; Abbott Molecular].

Radon Measurement. Indoor radon gas was measured with an alpha-track detector (CR-39; Radosys). Each patient received a study kit with (1) the detector to be placed in their home for 3 months, (2) an informational letter of instructions that explained how to use the device, (3) a sealed envelope to return the detector, and (4) a questionnaire to complete, including demographic data, home characteristics, smoking, and environmental exposure. All patients were contacted by phone at the beginning (day 3) and at end (day 93) of the measurement period to confirm the detector placement and removal, respectively. All detectors were placed under standard conditions and following the instructions provided to the patients. Basically, all of them were placed in the main bedroom off the floor (60-180 cm), away from doors, windows, and electrical devices. After the measurement period, the detectors were sealed and sent to the Galician Radon Laboratory of the School of Medicine at the University of Santiago de Compostela (Santiago de Compostela, Spain). Radon concentration was estimated taking into account the time the detector had been placed, with seasonal adjustment. This laboratory used quality controls and had taken part in the Spanish Radon Map, commissioned by the Nuclear Safety Council of Spain.

Pathologic Reevaluation. A lung cancer pathologist (A.B.) evaluated the pathologic features of all available tumor tissue samples. The morphologic features analyzed were histology subtype, histologic pattern, grade of differentiation, and/or the presence of necrosis, mucin, and inflammatory infiltrate.

Clinical Data and Collection Data. All data, including patient questionnaires, radon concentration report from the laboratory, and patient clinical, pathologic, and molecular characteristics, were prospectively collected.

Statistical Analysis

Descriptive analyses of radon distribution in the molecular subgroups, and bivariate analyses of concentrations and demographic, clinical, pathologic, and molecular features of the population were performed. Correlation and comparison studies of the radon concentration in each molecular subgroup were performed using parametric or nonparametric tests. $P < .05$ (bilateral) was considered statistically significant. Any adjustment of the significance level

Table 2 Baseline Home Characteristics and Measurement Characteristics of Population Study According to Molecular Subgroup

Characteristic	*EGFRm* (N = 36)	*ALKr* (N = 10)	*BRAFm* (N = 2)	Overall (N = 48)	*P*
Location					≤.001
Madrid	34 (94)	8 (80)	1 (50)	43 (90)	
Other	2 (6)	2 (20)	1 (50)	5 (10)	
Type of Housing					NS
Apartment	30 (83)	6 (60)	2 (100)	38 (79)	
House	6 (17)	4 (40)	0	10 (21)	
Building Material					NS
Brick	33 (92)	8 (80)	2 (100)	43 (90)	
Other	3 (8)	2 (20)	0	5 (10)	
Floor of building, median (range)	2 (0-15)	1 (1-5)	3 (2-5)	2 (0-15)	NS
Time living in current home (y), median (range)	38 (2-55)	15.5 (10-20)	36.5 (35-38)	28 (2-55)	.044
Time living in prior homes (y), median (range)	27 (4.2-84)	32 (3.5-56)	29 (—)	29 (3.5-84)	NS
Time out of home per year (mo), median (range)	1 (0-9)	1 (0-9)	2.5 (1-4)	1 (0-9)	NS
Season					NS
Winter	12 (33)	1 (10)	0	13 (27)	
Spring	1 (3)	1 (10)	0	2 (4)	
Summer	5 (14)	0	0	5 (10)	
Autumn	18 (50)	8 (80)	2 (100)	28 (58)	
Duration of measurement (d), median (range)	90 (82-123)	90 (90)	90 (90)	90 (82-123)	NS

Data are presented as n (%) unless otherwise indicated.
Abbreviations: *ALKr* = *ALK* rearranged; *BRAFm* = *BRAF* mutated; *EGFRm* = *EGFR* mutated; NS = not significant.

was performed to account for multiplicity of contrasts. We considered our hypothesis tests exploratory. Analyses were performed by SPSS Statistics 20 software (IBM, Armonk, NY).

Results

Fifty-three NSCLC patients were included between September 2014 and August 2015, five (9.4%) of whom were not eligible due to the absence of a molecular alteration (n = 2), missing detectors (n = 2), or invalid measurement (n = 1).

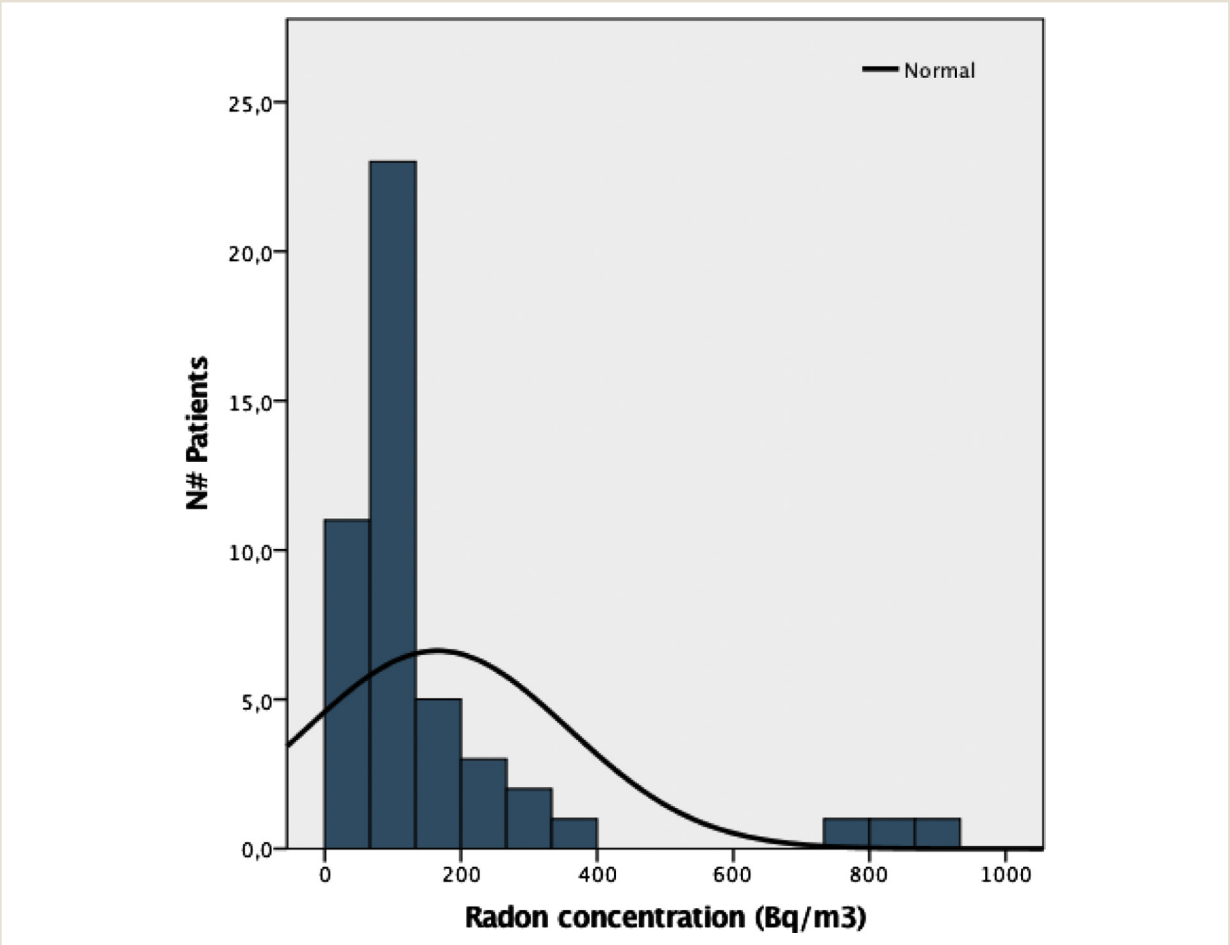
Table 1 summarizes the baseline characteristics of the overall study population (n = 48; *EGFR*, n = 36; *ALK*, n = 10; *BRAF*, n = 2) and according to molecular subgroup. The median age of the *ALK*-positive population was significantly lower compared to the other molecular subgroups (Kruskal-Wallis test, $P = .013$). The

Table 3 Indoor Radon Concentration According to Molecular Subgroup

Characteristic	*EGFRm* (N = 36)	*ALKr* (N = 10)	*BRAFm* (N = 2)	Overall (N = 48)	*P*
Indoor radon concentration (Bq/m^3), median (range)	96 (42-915)	116 (64-852)	125 (125)	104 (42-915)	.238
Indoor Radon Subgroup					.507
<50 Bq/m^3	2 (6)	0	0	2 (4)	
51-100 Bq/m^3	17 (47)	2 (20)	0	19 (40)	
101-150 Bq/m^3	9 (25)	4 (40)	2 (100)	15 (31)	
151-200 Bq/m^3	2 (6)	1 (10)	0	3 (6)	
201-250 Bq/m^3	1 (3)	1 (10)	0	2 (4)	
251-300 Bq/m^3	3 (8)	0	0	3 (6)	
>300 Bq/m^3	2 (6)	2 (20)	0	4 (8)	
WHO Indoor Radon Recommendation					.080
≤100 Bq/m^3	19 (53)	2 (20)	0	21 (44)	
>100 Bq/m^3	17 (47)	8 (80)	2 (100)	27 (56)	

Data are presented as n (%) unless otherwise indicated.
Abbreviations: *ALKr* = *ALK* rearranged; *BRAFm* = *BRAF* mutated; *EGFRm* = *EGFR* mutated; WHO = World Health Organization.

Figure 1 Distribution of Indoor Radon Concentration in Study Population



presence of signet ring cells (50%, n = 5; Fisher test, $P = .006$) was associated with *ALKr*. The presence of mucin (40%, n = 4; Fisher test, $P = .066$) was common in *ALKr* patients (Supplemental Table 1 in the online version). No other differences between *EGFR*, *ALK*, and *BRAF* subgroups were observed according to clinical and pathologic characteristics.

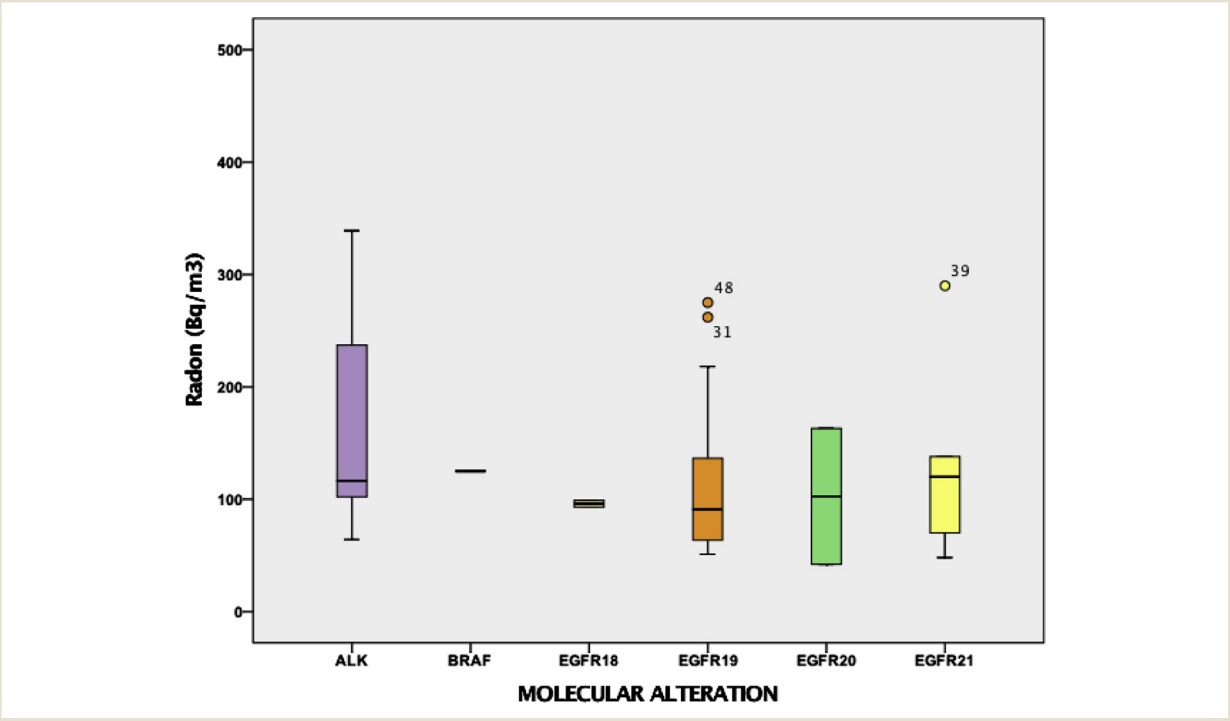
Table 2 shows patients' characteristics according to overall population and molecular subgroups. *ALK*-positive patients had been living for a shorter time in the home where the radon measurement was performed compared to the other two groups (Kruskal-Wallis test, $P = .044$). No other significant differences were observed.

Table 3 presents radon concentration overall and by molecular subgroup. Overall, the median indoor radon concentration was 104 Bq/m^3 (interquartile range [IQR], 69-160). A total of 27 patients (56%) presented concentrations above the WHO recommendation. Figure 1 shows the distribution of indoor radon concentration in the overall population. Home location (nonurban area) and type of housing (house) were associated with higher indoor radon levels (χ^2 test; $P. = \leq .001$, $P = .006$, respectively) (Supplemental Table 2 in the online version), with no significant differences between molecular groups for other home characteristics.

No significant differences were found between the median concentration of *EGFR*, *ALK*, and *BRAF* (Kruskal-Wallis test, $P = .238$). Figure 2 shows the distribution of indoor radon concentration by each molecular subgroup. Indoor radon concentration according to international and national recommendation is summarized in Supplemental Table 3 in the online version. Indoor radon concentrations above the WHO recommendation were reported in 80% (n = 8) of *ALK*-positive, 100% (n = 2) of *BRAF*-mutated, and 47% (n = 17) of *EGFR*-mutated (Fisher test, $P = .080$) patients. The presence of *ALK* and *BRAF* alterations versus *EGFRm* was associated with concentrations above WHO recommendation (Fisher test, $P = .044$). In the *EGFR* group, 5 (55%) of 9 of exon 21 subtype patients, 11 (47%) of 23 of exon 19 deletion subtype patients, 1 (50%) of 2 of exon 20 subtype patients, and 0 of 2 exon 18 patients had radon levels above WHO recommendations.

Nonmucinous tumors were more frequent in patients with lower concentrations of indoor radon (χ^2 test, $P = .009$). In contrast, well and moderately differentiated histologic grades were more frequent in patients exposed to higher concentrations (> 148 Bq/m^3) (χ^2 test, $P = .023$). Three of 4 patients with the highest

Figure 2 Box Diagram of Distribution of Indoor Radon Concentration According to Molecular Subtype



concentrations (> 296 Bq/m^3) had a papillary histologic pattern (Fisher test, $P = .023$).

Out of 15 smokers, active smoking at diagnosis (n = 5, 62.5%) was associated with a lower radon concentration ($P = .026$, Fisher test). No other associations were observed between indoor radon concentration and other baseline characteristics in the study population.

Discussion

Here we report the presence of indoor radon concentrations above the WHO recommendations in more than 50% of our population of *EGFRm*, *BRAFm*, and *ALKr* NSCLC patients analyzed prospectively. The median radon concentration was 104 Bq/m^3 (IQR 69-160), consistent with prior reports. Notably, the European pooled study by Darby et al[5] reported a median of indoor radon of 104 Bq/m^3 in lung cancer patients versus 97 Bq/m^3 in the control group. Long-period alpha track detectors were used, as recommended by WHO for measurements in dwellings,[2] and also took into consideration seasonal adjustment.

In our series, 73% of patients had radon concentrations above the US Environmental Protection Agency recommended level, for which an action against radon is recommended, and 23% of them had a concentration for which an action is necessary. The majority of the population (70%) had concentrations over the Spanish average, including 19% of cases with high-risk concentrations according to the Spanish Radon Map.

As previously reported, indoor radon can vary depending on several factors, such as the characteristics of the house. In our study, type of housing was significantly associated with higher radon levels, in agreement with prior reports.[2] No other home-related variables affected indoor radon concentrations. Although the city of Madrid is considered a low-risk area according to the Spanish Radon Map, in our series, we found high indoor radon levels. This could be because the risk groups are based on the mean of different areas, with high heterogeneity, and secondarily because we also enrolled patients from other surrounding areas.

On the basis of molecular alterations, we did not find significant differences between the indoor radon concentration of *EGFR*-, *BRAF*-, and *ALK*-positive NSCLC patients, with an overall median concentration of > 100 Bq/m^3. However, the *EGFR* subgroup median concentration was 96 Bq/m^3 (range, 42-915 Bq/m^3), which is 20 Bq/m^3 below the median of the two other subgroups. In addition, indoor radon concentrations above the WHO recommendation were the most common in the *ALK* and *BRAF* groups compared to the *EGFR* group.

Two studies assessing the same hypothesis have been reported. Taga et al[16] reported that indoor radon and environmental tobacco exposure (ETS) did not play a role in a cohort of nonsmoker lung cancer women from a nonprone area (*EGFR* mutated n = 24, median 43.5 Bq/m^3, vs. *EGFR* wild type n = 46, median 63.7 Bq/m^3).

Ruano-Raviña et al[17] published a retrospective analysis of cases comparing *EGFR*-mutant and -nonmutant, and *ALK*-positive versus -negative patients from a case series of never-smoking lung cancer patients from a radon-prone area. As in our study, the highest concentrations were observed in *ALK*-positive patients (12/80). The median radon concentration in *EGFR* patients was 160 Bq/m^3 (interquartilic range, 100-306), which is higher than that reported in our study, consistent with the areas where the two studies were performed.

However, data from 323 patients were retrospectively collected, and only 65% and 25% were tested for *EGFR* and *ALK*, respectively. In addition, no clinical or pathologic information was provided.

Our population was enriched but not limited to never-smoking patients, with 31% current or former smokers. These data correlate with large-scale studies in our country, such as the series published by Rosell et al,[18] in which > 33% of *EGFRm* patients were current or former smokers. Therefore, even though smoking could be a confounding factor in studies of radon and lung cancer, the expected influence in light smokers or longtime former smokers may be minimal.

We did not observe any differences when considering the specific *EGFR* sensitizing mutation, in contrast to the trend shown by Ruano-Raviña et al.[17] In our series, of 6 *EGFR* patients with concentrations > 200 Bq/m^3, 4 had exon 19 deletion and 2 had exon 21 mutations (L858R), but interestingly, no patients with exon 18 or 20 had concentrations of > 200 Bq/m^3. Both studies showed higher radon levels in *ALK*-rearranged patients, but with no significant differences, potentially due to the small sample sizes. Only 2 *BRAF* V600E−mutated patients were included in our study, which is insufficient to permit us to draw conclusions in this population, but no study has previously assessed radon related to *BRAFm*.

Interestingly, the Radon France study has recently reported the correlation of the prevalence of *EGFR, BRAF, KRAS, HER2, ALK*, and *ROS1* oncogenic alterations with the estimated indoor radon risk area based on the official French map (Institut de Radioprotection et de Sûreté Nucléaire, INSN, France) in a cohort of more than 100,000 NSCLC cases tested for *EGFR, BRAF, HER2, KRAS, ALK*, and *ROS1* on the 28 French Platform led by INCa (French National Cancer Institute).[19] The prevalence of driver alterations was higher in the French region with high radon exposure, consistent with our prospective findings. This represents the largest hypothesis-generating cohort reported to date about the role of indoor radon and lung cancer harboring driver alterations, but further confirmatory studies are needed because this study is based on the estimation of radon exposure risk and not in prospective measurements.

Pathologically, all patients in our study had adenocarcinoma histology, consistent with the predominant characteristics of nonsmokers or light smokers. Nonmucinous tumors were associated with lower concentrations. However, this finding may be influenced by *ALK*-positive patients, which constituted the patient group with high radon concentrations. Well- to moderately differentiated histologic grades were associated with higher radon concentrations. Although *ALK*-positive patients generally present tumors of high grade,[20] only 3 of 10 *ALK* patients in our study had disease of high histologic grade.

Interestingly, 3 (1 *EGFR* exon 19, 1 *EGFR* exon 21, and 1 *ALK*-positive patients) of the 4 patients exposed to the highest radon concentrations had a papillary histologic pattern. This pattern has been associated more frequently with *EGFRm*, but has been described in other molecular alterations.[20] To our knowledge, these pathologic findings have not previously been reported in radon-exposed lung cancer patients. However, as a result of the small sample size, multivariate analysis was not feasible. These findings merit further evaluation in larger studies.

Smoking is the main cause of lung cancer, and it is the principal confusing factor in radon studies, but our population mainly comprised nonsmokers. We assessed the role of ETS, but we did not see any association between indoor radon and ETS. In a nonsmoker population from a radon-prone area, Torres-Durán et al[21] suggested a nonsignificant risk increase of lung cancer when ETS was associated with > 200 Bq/m^3 indoor radon. However, there is no evidence supporting the increased risk of lung cancer when both risk factors are present, although this may be related to the difficulty of measuring ETS.

Our study has a number of limitations, in particular the small sample size and the lack of a control group with no molecular alterations on the assessed genes, which limit the conclusions that can be drawn. It is also important to note that half of our patients lived in a nonspecific radon-prone area. In addition, a change of residence was also common in our study population, with a median time spent in previous homes of 29 years. Taking into consideration that fact that the period of induction of lung cancer due to radon exposure is estimated to be between 5 and 25 years,[22] the measurements restricted to the current home can underestimate the accumulated indoor radon exposure. Additionally, the exposure in other places, such as the workplace, can also have an effect. Finally, although our study focused on the *EGFRm*, *BRAFm*, and *ALK*-positive population, there are described many other molecular alterations, mainly in nonsmoking patients, including *ROS1, RET*, and *NTRK1* rearrangements, some of them included in the Radon France study. Unfortunately, at the time this study was conducted, they were not routinely analyzed in our center, but they should be included in future studies.

Conclusion

Our study is to date the largest prospective assessment of the role of indoor radon on certain driver molecular populations, and on a small scale, it provides original and novel evidence that, together with previous studies, and the recently reported Radon France study, opens a new field of research with a potential major impact on both therapeutics and the prevention of lung cancer. To obtain solid evidence on this setting, large collaborative multidisciplinary studies with a control group are needed to thoroughly assess the role of indoor radon combined or not with other risk factors in NSCLC patients with driver molecular alterations. The development of novel and accessible molecular diagnostic platforms, such as next-generation sequencing techniques that analyze simultaneously multiple molecular alterations, could better characterize this population, simplifying future studies about indoor radon.

Our study showed median indoor radon concentration above the WHO recommendation (> 100 Bq/m^3) in a population of *EGFRm, ALKr*, and *BRAFm* NSCLC patients, with no differences between the 3 molecular groups. The concentrations above the WHO recommendation were most common in *ALKr* and *BRAFm* patients. These findings should be validated in larger studies.

Clinical Practice Points

- Radon is a radioactive gas derived from the uranium decay chain, considered to be first cause of lung cancer in nonsmokers by WHO, which recommends it not exceed 100 Bq/m^3 in homes. Unfortunately, radon exposure is not homogeneously regulated worldwide. In parallel, several driver oncogenic alterations have been described, mainly in nonsmoker NSCLC patients, with no risk factor yet identified.
- We prospectively studied indoor radon concentrations in 48 *EGFRm* or *BRAFm* mutations and *ALKr* NSCLC patients. We

found a median concentration of radon above the WHO recommendation, with no differences between the 3 molecular groups. However, the radon concentrations above the WHO recommendation were most common in *ALK*- and *BRAF*-positive patients.

- This study is the first prospective hypothesis-generating study about the link between driver alterations and indoor radon as a lung cancer risk factor, showing levels above WHO recommendation in *EGFRm*, *ALKr*, and for first time to our knowledge, *BRAFm* patients.
- To date, our work is the largest prospective assessment on these driver populations, and on a small scale, it provides original evidence that, taken together with previous work, including the recently reported Radon France study, opens a new field of research with a potential major impact in both therapeutics and lung cancer prevention.
- Radon gas is an environmental and potentially preventable risk factor; studies such as ours can help raise awareness about radon-related lung cancer, making this invisible risk factor more real.

Acknowledgment

The authors thank Sarah MacKenzie, PhD, for English-language editing. They thank the team of the Medical Oncology Department and the Thoracic Oncology Committee, at the Ramón y Cajal Hospital (Madrid, Spain).

Disclosure

The authors have stated that they have no conflict of interest.

Supplemental Data

Supplemental tables accompanying this article can be found in the online version at https://doi.org/10.1016/j.cllc.2019.04.009.

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Supplemental Data

Supplemental Table 1 Pathologic Characteristics According to Molecular Subgroup

Characteristic	*EGFRm* (N = 36)	*ALKr* (N = 10)	*BRAFm* (N = 2)	Overall (N = 48)	*P*
Histologic Grade					
Well differentiated	3 (8)	1 (10)	0	4 (8)	NS
Moderately differentiated	19 (53)	5 (50)	0	24 (50)	
Poorly differentiated	10 (28)	3 (30)	1 (50)	14 (29)	
Unknown	4 (11)	1 (10)	1 (50)	6 (13)	
Histology Pattern					
Mixed	14 (39)	3 (30)	0	17 (35)	NS
Acinar	14 (39)	5 (50)	0	19 (40)	
Solid	4 (11)	3 (30)	0	7 (15)	
Papillary	11 (31)	2 (20)	0	13 (27)	
Micropapillary	10 (28)	2 (20)	1 (50)	13 (27)	
Lepidic	4 (11)	0	0	4 (8)	
Bronchioalveolar	1 (3)	0	1 (50)	2 (5)	
Unknown	4 (11)	1 (10)	0	5 (10)	
Presence of Mucin					
No	29 (81)	5 (50)	2 (100)	36 (75)	.066
Yes	4 (11)	4 (40)	0	8 (17)	
Unknown	3 (8)	1 (10)	0	4 (8)	
Carcinomatous Lymphangitis					
No	21 (58)	5 (50)	0	26 (54)	NS
Yes	11 (31)	4 (40)	1 (50)	16 (33)	
Unknown	4 (11)	1 (10)	1 (50)	6 (13)	
Seal Ring Cells					
No	30 (83.4)	4 (40)	1 (50)	35 (73)	.006
Yes	3 (8.3)	5 (50)	0	8 (17)	
Unknown		1 (10)	1 (50)	5 (10)	
Inflammatory Infiltrate					
No	8 (22)	4 (40)	1 (50)	13 (27)	NS
Yes	23 (64)	5 (50)	0	28 (58)	
Unknown	5 (14)	1 (10)	1 (50)	7 (15)	

Data are presented as n (%).
Abbreviations: *ALKr* = *ALK* rearranged; *BRAFm* = *BRAF* mutated; *EGFRm* = *EGFR* mutated.

Supplemental Table 2 Home Characteristics According to Indoor Radon Subgroup

Characteristic	< 50 Bq/m^3 (N = 2)	51-100 Bq/m^3 (N = 19)	101-150 Bq/m^3 (N = 15)	151-200 Bq/m^3 (N = 3)	201-250 Bq/m^3 (N = 2)	251-300 Bq/m^3 (N = 3)	> 300 Bq/m^3 (N = 4)	Overall (N = 48)	*P*
Location									
Urban area	1 (50)	19 (100)	14 (93)	3 (100)	2 (100)	3 (100)	1 (25)	43 (90)	≤.001
Nonurban area	1 (50)	0	1 (7)	0	0	0	3 (75)	5 (10)	
Type of Housing									
Apartment	2 (100)	15 (79)	14 (93)	2 (67)	1 (50)	3 (100)	1 (25)	38 (79)	.006
House	0	4 (21)	1 (7)	1 (33)	1 (50)	0	3 (75)	10 (21)	
Building Material									
Brick	2 (100)	18 (95)	13 (87)	3 (100)	1 (50)	3 (100)	3 (75)	43 (90)	NS
Other	0	1 (5)	2 (13)	0	1 (50)	0	1 (25)	5 (10)	
Age of Building									
<10 y	0	2 (10.5)	1 (6.7)	0	0	0	0	3 (6)	
11-20 y	1 (50)	6 (31.5)	4 (26.6)	1 (33)	1 (50)	0	1 (25)	14 (29)	NS
>20 y	1 (50)	8 (42)	9 (60)	2 (67)	1 (50)	3 (100)	3 (75)	27 (56)	
Unknown	0	3 (16)	1 (6.7)	0	0	0	0	4 (8)	
Floor of Building									
0-1	1 (50)	7 (37)	3 (20)	2 (67)	2 (100)	0	4 (100)	19 (40)	NS
2-3	1 (50)	7 (37)	7 (47)	1 (33)	0	1 (33)	0	17 (35)	
>3	0	3 (16)	5 (33)	0	0	2 (67)	0	10 (21)	
Unknown	0	2 (10)	0	0	0	0	0	2 (4)	
Time Living in House									NS
<10 y	1 (50)	4 (21)	2 (13)	0	0	0	0	7 (15)	
11-20 y	1 (50)	8 (42)	3 (20)	1 (33)	2 (100)	0	1 (25)	16 (33)	
>20 y	0	4 (21)	8 (53)	2 (67)	0	2 (67)	2 (50)	18 (38)	
Unknown years	0	3 (16)	2 (13)	0	0	1 (33)	1 (25)	7 (14)	

Data are presented as n (%) unless otherwise indicated.
Abbreviation: NS = not significant.

Supplemental Table 3 Radon Concentration According to International and National (Spain) Recommendations

Recommendation	*EGFR* (N = 36)	*ALK* (N = 10)	*BRAF* (N = 2)	Total (N = 48)	*P* (χ^2)
WHO					
<100 Bq/m^3	19 (53)	2 (20)	0	21 (44)	.080
>100 Bq/m^3	17 (47)	8 (80)	2 (100)	27 (56)	
EURATOM					
<300 Bq/m^3	34 (94)	8 (80)	2 (100)	44 (92)	NS
>300 Bq/m^3	2 (6)	2 (20)	0	4 (8)	
EPA					
<74 Bq/m^3, low risk	12 (33)	1 (10)	0	13 (27)	NS
74-148 Bq/m^3, intermediate	15 (42)	5 (50)	2 (100)	22 (46)	
>148 Bq/m^3, high risk	9 (25)	4 (40)	0	13 (27)	
Spanish Radon Map					
<150 Bq/m^3, low risk	28 (78)	6 (60)	2 (100)	34 (71)	NS
150-200 Bq/m^3, intermediate	2 (5)	1 (10)	0	3 (6)	
>200 Bq/m^3, high risk	6 (17)	3 (30)	0	9 (19)	

Data are presented as n (%).
Abbreviations: EPA = US Environmental Protection Agency; EUTAROM = European Atomic Energy Community; NS = not significant; WHO = World Health Organization.