

## Editorial

# Residential Radon and Risk of Lung Cancer in Never-Smokers<sup>☆</sup>



## Radón residencial y riesgo de cáncer de pulmón en nunca fumadores

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Scientific evidence suggests that lung cancer (LC) in never-smokers is a different molecular entity to LC in smokers.<sup>1,2</sup> The Lung Cancer Risk in Never-Smokers (LCRINS) study, a multicenter case control study competitively funded by the Government of Galicia, began in January 2011. Ten hospitals participated in 3 autonomous communities (Galicia, Asturias, and Madrid). The aim of the study was to determine LC risk factors in never-smokers, looking particularly at residential radon, and the initial results were published in ARCHIVOS DE BRONCONEUMOLOGÍA in 2012.<sup>3</sup>

Six years later, this study has recruited more than 400 cases of LC in never-smokers with an equal number of controls, making it an important source of epidemiological data in this subgroup of LC cases. Moreover, the study provides a model that might serve as a basis for other multicenter studies, a highly desirable design in the investigation of rare diseases. The main findings of the LCRINS study, focusing primarily on residential radon, are highlighted and discussed below.

Residential radon is the second most important risk factor for LC after smoking, and the most important in never-smokers.<sup>4</sup> Other significant risk factors for LC include certain occupations that involve exposure primarily to asbestos, polycyclic aromatic hydrocarbons (diesel exhaust), silica dust, or heavy metals, and environmental exposure to tobacco. However, only a small proportion of the population is employed in risk occupations (a risk that has decreased since environmental exposure to tobacco smoke among workers in the bar and restaurant sector has been eliminated). Environmental exposure to tobacco smoke is a quantitatively smaller risk than indoor radon, and is less ubiquitous.

Galicia, along with regions of Madrid, Extremadura and Castile-Leon, are areas with high radon concentrations, due to the geological characteristics of the subsoil. Other studies have suggested that the greatest numbers of cases of LC in female

never-smokers occurred in the province of Ourense, which may be due to exposure to indoor radon, although this was not measured.<sup>5</sup>

The World Health Organization sets the action level of radon at 100 Bq per cubic meter,<sup>4</sup> while the United States Environmental Protection Agency sets it at 148 Bq per cubic meter.<sup>6</sup> The action level is understood as the lowest concentration at which radon significantly increases the risk of LC. These risk levels are based on a European study that included over 7000 cases and 14000 controls and revealed a significant linear risk of developing LC due to exposure to residential radon, namely, a 16% increase in risk per 100 Bq/m<sup>3</sup> increase in indoor radon concentration.<sup>7</sup>

Most of the research performed on residential radon before the start of the LCRINS study had included cases of LC in smokers and former smokers. The LCRINS study confirmed that the risk of LC was also greater in never-smokers, and that this risk was significant at concentrations higher than 200 Bq per cubic meter<sup>8</sup> compared to the risk in subjects exposed to less than 100 Bq per cubic meter (OR: 2.42; 95% CI: 1.45–4.06), indicating that radon is a risk factor for LC. These results suggest that to induce LC, never-smokers must be exposed to higher radon concentrations than smokers. This study also showed evidence of an interaction between residential radon and environmental exposure to tobacco smoke. A detailed analysis of the cases reveals that subjects diagnosed before the age of 60 years were exposed to a higher concentration of residential radon than those diagnosed at older ages, suggesting that exposure to a very high concentration of radon could cause LC to develop earlier.<sup>9</sup> Our analysis of histological types showed that residential radon appears to be more closely associated with small cell cancer and other less common histological types, such as large cell LC. Nevertheless, exposure to radon is associated with all histological types of LC in never-smokers.<sup>10,11</sup>

The LCRINS study also showed that there may be an association between residential radon and mutations or alterations in LC driver genes. We found no differences in residential radon concentrations between patients with and without EGFR mutations, but we did find close to significant differences in radon exposure in patients with the exon 19 deletion compared to patients with the L858R single-point substitution mutation, who were less exposed to radon ( $P=.057$ ). We also found that subjects with ALK translocation had almost twice the radon exposure as subjects without ALK

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translocation, although the results were not significant<sup>12</sup> (the proportion of ALK-positive subjects is low). We will have to wait for the results of future studies to see if these findings are confirmed or not.

Genes conferring sensitivity to LC, such as GSTM1 and GSTT1, seem to modulate exposure to residential radon to a certain extent, and, similar to findings in smokers, studies performed in Galicia and other regions indicate that subjects with any of these gene deletions exposed to the same concentrations of radon had a greater risk of lung cancer.<sup>13,14</sup>

In view of the accumulated evidence, we propose that scales predicting the risk of LC death or incidence should include exposure to radon, in addition to tobacco consumption and the many other variables that are already included, but which do not show the same degree of causal association as seen for residential radon.<sup>15</sup>

Radon is a risk factor for LC, both in smokers and never-smokers. It should be considered as a cause of LC when this disease is detected in a never-smoker, particularly in areas with high exposure to radon. From a practical point of view, studies such as this highlight the usefulness of multicenter research in respiratory medicine for relatively unusual diseases such as LC in never-smokers or small cell LC, in which we began a similar study in 2015.

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