Alpha-1 Antitrypsin Deficiency and Lung Cancer Risk

A Case–Control Study in Never-Smokers

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Background: Never-smokers comprise up to 25% of all lung cancer cases. They could have different molecular pathways for lung cancer induction compared with smokers. Alpha-1 antitrypsin (AAT) deficiency is a hereditary trait whose main characteristic is early onset of lung emphysema. Our aim is to know if AAT-deficient carriers have a higher risk of lung cancer in a study performed exclusively in never-smokers.

Methods: We designed a multicentre hospital-based case–control study, which included incident never-smoking lung cancer cases. Controls were never-smokers attending nonmajor surgery at the participating hospitals. Controls were frequency matched on age and gender with cases. We determined AAT variants (alleles S and Z) through polymerase chain reaction.

Results: Two hundred and twelve cases and 318 controls were included. PiSS individuals showed a lung cancer risk of 4.64 (95% confidence interval: 1.08–19.92) compared with those with normal genotype (PiMM). When the analysis was restricted to women, the risk for PiSS increased to 7.58 (95% confidence interval: 1.40–40.87). This risk for homozygous SS was even higher for individuals exposed to environmental tobacco smoke (greater than 20 years). The presence of other alleles did not show any effect on lung cancer risk.

Conclusions: Never smoking SS homozygous individuals pose an increased risk of lung cancer. The risk is higher for individuals exposed to environmental tobacco smoke.

Key Words: Lung cancer, Alpha-1 antitrypsin deficiency, Never-smokers, Environmental tobacco smoke, Residential radon.

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Lung cancer is a worldwide health problem. It is currently the leading cause of cancer death.[1] Although the main risk factor is tobacco consumption, up to 25% of all cases are diagnosed in never-smokers, with important geographic variations.[2] The most important risk factor in never-smokers is residential radon.[3,4] Lung cancer in never-smokers has been proposed as a different disease than lung cancer occurring in ever-smokers due to different molecular pathways.[5,6] Nevertheless, the available studies are still scarce.

Alpha-1 antitrypsin deficiency (AATD) is a hereditary condition first described by Laurell and Eriksson.[7] Alpha-1 antitrypsin (AAT) is a glycoprotein codified by SERPINE1 gen, placed in the long arm of chromosome 14. It is synthesized mainly in the liver and its main function is to inhibit neutrophil elasthase and other serine proteases. It provides more than 90% of the total antiprotease capacity of the organism[8] and, in the past years, it has been described that it has anti-inflammatory[9] and inmunomodulatory[10] properties, among others.

AAT gene comprises two alleles that are transmitted through a codominant autosomic Mendelian pattern. Wild alleles are named M and are present in 85%–90% of individuals (MM). The most frequent deficient alleles are called S and Z and are present in 10% and 2% of Spanish population, respectively,[11] although there are very few published studies.

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The severity of the deficiency is related to the deficient allele. The S allele expresses around 40% of AAT and the Z allele expresses around 15%.

The main AATD clinical symptom is the early development of lung emphysema, mainly in individuals exposed to tobacco smoke. It is also known its association with bronchiectasis, panniculitis, and ANCA+ vasculitis. Some investigations have been published in the past years associating AATD with fibromyalgia or asthma.[12–14]

The imbalance protease–antiprotease originated from the low AAT concentration in blood and tissues causes a lower protection against proteases, being the most important neutrophil elastase, and is the cause of the harm that finally produces lung emphysema secondary to AATD. These alterations could favor the hypothesis of lung carcinogenesis.

Some investigations have assessed the possible relation between AATD and the risk of lung cancer, with opposite results.[15–18] All these studies have included a high percentage of smokers and exsmokers, and there is no study performed exclusively in never-smokers. A study performed in never-smokers would eliminate the possible distortion caused by tobacco consumption and therefore increase the validity of the study results. This advantage would be greater should the study retrieved information on residential radon and environmental tobacco smoke.

The aim of this study is to analyze if it exists an association between deficient AAT alleles, carried in homozygosis or heterozygosis and the risk of lung cancer in never-smokers. As a secondary objective, we aim to know if AATD could pose more risk in individuals exposed to environmental tobacco smoke for more than 20 years versus those exposed during a shorter period.

PATIENTS AND METHODS

We designed a multicentre hospital-based case–control study. Seven Galician hospitals and one in Asturias took part. Cases were all never-smoking lung cancer cases diagnosed at the participating hospitals between January 2011 and December 2013. Controls were never-smoking individuals who undergone nononcologic surgery, mainly major ambulatory surgery. To be classified as a never-smoker, we used the definition of the World Health Organization: to have smoked less than 100 cigarettes in lifetime or having smoked less than 1 cig/day during 6 months. Controls were frequency-matched with cases on age and gender.

All participants were interviewed on their lifestyle, with special emphasis on environmental tobacco smoke exposure, previous occupations, leisure time activities, and diet and alcohol consumption. We measured residential radon in most participants' homes after giving them a radon detector. The device was placed in the main bedroom at least during 3 months. Environmental tobacco smoke exposure was defined as having lived with a smoker at least during the past 20 years. Exposed individuals were asked about the relationship with the smoker/s at the same dwelling, years of living, and number of daily cigarettes smoked by the cohabitant.

We searched for significant airflow obstruction in clinical records of all patients with AATD (homozygous SS or ZZ, and heterozygous MS, MZ, or SZ) and also searched for emphysema using lung computed tomography images. This information allowed us to rule out COPD or emphysema in these AATD lung cancer patients.

Participants also donated 3 ml of total blood that was used to determine certain genetic polymorphisms, including deficient alleles for AAT S and Z, through analyzing the genotype. All samples were analyzed at the National Genotyping Center at the University of Santiago de Compostela. This facility has the most advanced techniques combined with rigorous quality control procedures.

Genotyping was performed using the MassARRAY iPLEX GOLD SNP genotyping system (Sequenom Inc., San Diego, CA), following the manufacturer's instructions. The principles of this method are detailed in Buetow et al.[19]

The study protocol was approved by the Galician Ethics Committee (2010/295) and all participants signed a written consent to participate in this research.

Statistical Analysis

We first performed a univariate and bivariate analysis, describing the characteristics of cases and controls regarding age, gender, exposure to environmental tobacco smoke, and residential radon. Afterwards, we performed a logistic regression where the dependent variable was the case or control status and the main independent variable being a carrier of S or Z alleles in homozygosis or heterozygosis. We did the same analysis for women (but not for men due to the low number on included males) and finally we analyzed if the risk of lung cancer for the deficient AAT alleles was different depending on having being exposed or not to environmental tobacco smoke during the past 20 years. The results are expressed as ORs with 95% confidence intervals. The analysis was performed with SPSS version 20.

RESULTS

Two hundred and twelve cases and 318 controls were included. Table 1 shows the sample characteristics.

The median age of cases and controls was similar and also gender distribution, 81.8% of cases were women versus 78.7% of controls. Residential radon exposure was available for 175 cases (82.5%) and 270 controls (84.9%). Of them, 48% of cases were exposed to radon concentrations higher than 200 Bq/m^3 compared with 30.4% of controls. The predominant histological type was adenocarcinoma (77.7%) followed by squamous cell carcinoma (9.5%). We included 63 AAT-deficient cases. All these cases except one had a lung CT scan. We did not find any case of lung emphysema and only in three cases localized bronchiectasis were described. Lung function tests were available in 26 of 63 AATD cases. In those cases with spirometry, it was normal in 19, it was obstructive in three cases and it showed a nonobstructive pattern in four cases. These three patients were, respectively, MS, MZ, and SS. 22.6% of cases had a heterozygous allele S compared with 29.9% of controls. Seven cases (3.3%) and three controls (0.9%) were homozygous SS. Heterozygous Z carriers were observed in 11 cases (5.2%) and 16 controls (5%). There were no ZZ homozygous individuals. The distribution of the different combinations of alleles and their risk of lung cancer is shown in Table 2.