

Editorial

Lung Cancer and Emphysema[☆]

Cáncer de pulmón y enfisema

Jessica Gonzalez, Juan P. de-Torres*

Departamento de Neumología, Clínica Universidad de Navarra, Pamplona, Navarra, Spain



Lung cancer (LC) is the most common cause of cancer death in men and women.¹ Since it is often diagnosed at advanced stages, estimates suggest that it will still be one of the major causes of death in 2030. Recent studies using low-dose computed tomography (LDCT) have found that emphysema is one of the main risk factors for developing LC.

Emphysema has traditionally been diagnosed in the pathology laboratory.² Now, the presence, severity and distribution of this process can be identified non-invasively with the use of LDCT. Thanks to computerized analytical techniques, the grade of emphysema can now also be quantified, even before changes in respiratory function are detected. de Torres et al.³ were the first to report that patients with emphysema detected visually on CT had a 3-fold higher risk of LC than patients without emphysema, irrespective of the presence of COPD. The Pittsburg Lung Screening (PLuSS) cohort, in which emphysema was also determined visually, obtained similar results (RR: 3.56; 95% CI: 2.21–5.73).⁴

The evidence indicates that the presence and severity of emphysema on LDCT are significantly associated with LC. Quantification software is now available that automatically determines the presence and severity of emphysema. Smith et al.⁵ performed a meta-analysis of 7 studies that explored the association between emphysema and the risk of LC, and compared the visual qualitative measurement with the automatic measurement made by the software. Visually detected emphysema was the only factor associated with the risk of developing LC. Some controversy has arisen with regard to the severity of emphysema and its relationship with LC, since a non-linear relationship was found, and only in those studies in which emphysema was determined visually.

The association between emphysema and the risk of LC is also observed in individuals who have never smoked. Investigators in the International I-ELCAP study compared the prevalence of LC in smokers, former smokers and never-smokers screened for LC using LDCT.⁶ The authors found a similar prevalence of LC in smokers with emphysema and non-smokers with emphysema (2.1% and 2.6%, respectively; $P=.61$). The multivariate analysis showed that

the presence of emphysema in non-smokers significantly increased the risk of LC (OR: 6.3; 95% CI: 2.4–19.9). This association was supported by Torres-Durán et al.,⁷ who analyzed 212 cases of LC with a 30% prevalence of alpha-1 antitrypsin (A1AT) deficiency. They found that the homozygous SS genotype was associated with a greater risk of LC, although none of the patients had emphysema on CT, suggesting that not only emphysema but also A1AT deficiency is related with the risk of developing LC.

Several mechanisms have been proposed to explain the association between emphysema and LC, all of which point to tobacco use as the major cause. With each inhalation of smoke, over 4000 products are released, generating reactive oxygen species that subsequently produce oxidative stress and chronic inflammation in the lung that persist after giving up smoking. This leads to an imbalance between the production of proteinases that degrade the cell matrix and the action of anti-proteinases, leading to the activation of the inflammatory cascade and the release of inflammatory mediators by the neutrophils, lymphocytes and macrophages. This uncontrolled chronic inflammation can cause cell apoptosis, but it can also trigger reparative phenomena, as the bronchoalveolar stem cells associated with the basal membrane attempt to repair the damage.⁸ Due to chronic inflammation and continual insult, these cells are permanently under pressure to proliferate, repopulate and repair the damaged lung – and there is a thin line between uncontrolled proliferation and the generation of carcinogenic mutations. In patients with emphysema, mucociliary clearance is affected, so carcinogens accumulate in the lung and come into close contact with tissues. In these emphysematous areas, moreover, alveolar oxygenation levels are lower, inducing the expression of hypoxia-inducible factors (HIF) associated with the development of LC. Finally, reports have appeared in the literature of genes linked to emphysema that can also be a factor in developing lung cancer, irrespective of the subject's smoking habit. These include different mechanisms: epigenetic factors, altered microRNA regulation, telomere shortening, and adaptive immune response.

Recently, a screening score for LC (LUCSS) was proposed and validated for identifying high-risk COPD patients in 2 screening cohorts in Spain (P-IELCAP) and the United States (PLuSS), which include age, body mass index, pack-year index, and emphysema visualized on LDCT.⁹ Patients are classified into 2 categories: low risk (0–6 points) or high risk (≥ 7 points). The latter have a risk of

[☆] Please cite this article as: Gonzalez J, de-Torres JP. Cáncer de pulmón y enfisema. Arch Bronconeumol. 2017;53:47–48.

* Corresponding author.

E-mail address: jpdetorres@unav.es (J.P. de-Torres).

diagnosis of LC 3-fold higher than that of low-risk patients (RR: 3.5; 95% CI: 1.7–7.1). To facilitate the use of a scoring system in the clinic and to obviate the need for a LDCT, a new scoring system, called the COPD-LUCSS-DLCO, has been proposed in which emphysema on imaging tests is replaced by the diffusing capacity of the lung for carbon monoxide (DLCO). This system is used to classify patients into low risk (0–3 points) and high risk (3.5–8 points). This latter group has a 2.4-fold risk of death from LC compared to the low-risk group (95% CI: 2.0–2.7).¹⁰

The most significant message is that radiological emphysema is posited as one of the most potent biomarkers associated with the risk of developing LC. Specific screening for emphysema in at-risk populations is justified because it can be used to classify risk in our patients who smoke, either with clinical indexes that include the performance of an LDCT or else with functional tests, such as DLCO.

Funding

Funding for the preparation of this manuscript was received from the following agencies: Thematic Network for Cooperative Research on Cancer, Instituto de Salud Carlos III, Ministry of Economics and Competitiveness and the European Regional Development Fund (ERDF) “*Una manera de hacer Europa*”; and Projects PI04/2404, PI07/0792, PI10/01652, PI11/01626, of the Instituto de Salud Carlos III, Ministry of Economics and Competitiveness, Spanish Government.

References

1. Naghavi M, Wang H, Lozano R, Davis A, Liang X, Zhou M, et al. Global, regional, and national age–sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2015;386:2287–323.
2. Anderson AE, Hernández JA, Eckert P, Foraker AG. Emphysema in lung macrosections correlated with smoking habits. *Science*. 1964;144:1025–6.
3. de Torres JP, Bastarrika G, Wisnivesky JP, Alcaide AB, Campo A, Seijo LM, et al. Assessing the relationship between lung cancer risk and emphysema detected on low-dose CT of the chest. *Chest*. 2007;132:1932–8.
4. Wilson DO, Weissfeld JL, Balkan A, Schragin JG, Fuhrman CR, Fisher SN, et al. Association of radiographic emphysema and airflow obstruction with lung cancer. *Am J Respir Crit Care Med*. 2008;178:738–44.
5. Smith BM, Pinto L, Ezer N, Sverzellati N, Muro S, Schwartzman K. Emphysema detected on computed tomography and risk of lung cancer: a systematic review and meta-analysis. *Lung Cancer*. 2012;77:58–63.
6. Henschke CI, Yip R, Boffetta P, Markowitz S, Miller A, Hanaoka T, et al. CT screening for lung cancer: importance of emphysema for never smokers and smokers. *Lung Cancer*. 2015;88:42–7.
7. Torres-Durán M, Ruano-Ravina A, Parente-Lamelas I, Abal-Arca J, Leiro-Fernández V, Montero-Martínez C, et al. Alpha-1 antitrypsin deficiency and lung cancer risk: a case–control study in never-smokers. *J Thorac Oncol*. 2015;10:1279–84.
8. Houghton AM. Mechanistic links between COPD and lung cancer. *Nat Rev Cancer*. 2013;13:233–45.
9. de-Torres JP, Wilson DO, Sánchez-Salcedo P, Weissfeld JL, Berto J, Campo A, et al. Lung cancer in patients with chronic obstructive pulmonary disease. Development and validation of the COPD Lung Cancer Screening Score. *Am J Respir Crit Care Med*. 2015;191:285–91.
10. de-Torres JP, Marín JM, Casanova C, Pinto-Plata V, Divo M, Cote C, et al. Identification of COPD patients at high risk for lung cancer mortality using the COPD-LUCSS-DLCO. *Chest*. 2016;149:936–42.