

Chronic Obstructive Pulmonary Disease and Lung Cancer

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The prevalence of chronic obstructive pulmonary disease (COPD) is estimated at between 9% and 10% in the general Spanish population¹ and is presumably even higher in those aged over 65 years. COPD is characterized by the presence of a progressive obstruction of the airways that is not completely reversible and that is associated with an abnormal inflammatory response of the lungs and the airways to harmful particles and gases. The most common cause is smoking. In fact, it has been reported that smoking cessation and oxygen therapy increase survival in patients with COPD.^{2,3} The beneficial effects of quitting smoking are also known to include fewer deaths due to COPD-associated cardiovascular disease and a lower incidence of lung cancer,² which is between 2- and 5-fold greater than in smokers without the disease. COPD has actually been shown to be an independent risk factor for lung cancer,^{4,6} and together these 2 diseases have recently been reported to be the biggest contributors to deaths attributable to smoking.⁷

Several studies are currently investigating the comorbidities associated with COPD in view of the high impact of such conditions on mortality in COPD patients. The traditional definition of comorbidity, that is, the coexistence of another disease alongside the primary disease under study, has fallen into disuse. In the case of COPD, this definition has been questioned given that certain comorbidities such as lung cancer, cardiovascular diseases, and osteoporosis may be a consequence of the underlying disease itself. Several studies whose primary objective was to analyze the causes of death in different cohorts of patients with COPD in different stages of the disease have found that lung cancer and cardiovascular diseases are the most frequent causes of death in patients with mild or moderate disease, whereas respiratory failure is the most common in those with advanced disease.⁸

As mentioned, COPD is an independent risk factor for lung cancer.^{4,6} A number of studies have served as the basis for this affirmation. For example, it has been reported that the incidence of lung cancer is between 2 to 5 times greater in smokers with chronic bronchitis or emphysema than in smokers without COPD.⁹⁻¹¹ In addition, an inverse relationship between the degree of airway obstruction and the risk of lung cancer has been demonstrated.¹⁰ The mechanisms by which the risk of developing neoplastic disease increases with COPD are not clear, although it is accepted that chronic inflammation probably plays a role in the pathogenesis of lung cancer in these patients. Several chronic inflammatory diseases in other organs have also been shown to provide a favorable pathologic substrate for the subsequent development of cancer. For example, chronic pancreatitis has been linked with pancreatic cancer, Barrett esophagus with esophageal cancer, and inflammatory bowel disease with colon cancer.

Experimental studies have shown that cigarette smoke increases the expression of certain inflammatory cytokines, which, in turn, promote the inflammatory response of lymphocytes through induction of the cyclooxygenase-2 enzyme, thereby leading to the production of cytokines such as interleukin (IL) 6, IL-8, and IL-10, among others.^{12,13} Some of these cytokines can inhibit apoptosis, interfere in cell repair mechanisms, and promote angiogenesis. Mounting evidence therefore suggests that chronic inflammation is probably essential to enhancing the initial mutagenic process and favor tumor growth (by creating a proangiogenic environment) and metastasis. Moreover, these cytokines have also been implicated in COPD progression and in the development of the systemic effects, such as muscular dysfunction and weight loss suffered by some patients. It is of interest to highlight that chronic inflammation of the airways persists for many years after the individual has quit smoking. Indeed this inflammation is probably the pathophysiologic mechanism underlying the high risk of suffering lung cancer, even though the patient may have quit years before.

Another essential cytokine or growth factor for tumor growth is vascular endothelial growth factor (VEGF), which, along with angiopoietins and ephrins, is one of the most potent regulators of angiogenesis. The expression of VEGF in tissue is regulated by several factors such as

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hypoxia, other growth factors, such as epidermal growth factor, transforming growth factor β_1 , and insulin growth factor, and a number of other cytokines. It should be stressed that VEGF is induced by the binding of hypoxia inducible factor to a specific site on the promotor region of VEGF itself. Several studies in patients with COPD have shown that VEGF levels were elevated in the bronchial tree, alveolar macrophages, and the smooth muscle cells of the airways.¹⁴ In addition, in patients with lung cancer, VEGF levels were elevated in blood and also correlated with poorer survival.¹⁴ In fact, it has been established that this factor could be used as a good indicator of the angiogenic potential of a tumor, as well as its biologic aggressiveness.¹⁵ Increased levels of VEGF receptors have also been seen in cancer cells from patients with lung cancer.¹⁶

Another of the mechanisms potentially implicated in the development of lung cancer in patients with COPD is increased bronchial, systemic, and muscular oxidative and nitrosative stress—which is a characteristic of such patients.¹⁷⁻²⁰ Furthermore, both the gaseous and solid components of cigarette smoke in themselves lead to an increase in the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), as well as activation of inflammatory cells (leukocytes), which in turn may contribute to increased local and systemic oxidant levels. Excessive oxidant production that is not neutralized by tissue antioxidant systems (that is, oxidative and nitrosative stress) induces structural and functional changes in other cell components such as lipids, proteins, and DNA, with a negative impact on all the signaling cascades and metabolic pathways dependent on these components. Proteins are a target molecule for the action of excess oxidants in tissue. An increase in oxidative and nitrosative stress was reported in the blood of patients with lung cancer; proteins modified by ROS and RNS, such as fibrinogen, transferrin, plasminogen, and ceruloplasmin, were also detected.²¹ In another more recent study, an increase in nitrosative stress was demonstrated (by immunohistochemical techniques) in the region of the tumor compared to the uninvolved surrounding tissue in patients without COPD.²² That same study managed to identify (by proteomic techniques) proteins modified by excess RNS in the region of the tumor. The most noteworthy of these proteins turned out to be antioxidants, enzymes implicated in glucose and lipid metabolism, proteins implicated in apoptosis, and structural proteins. The authors concluded that the oxidant species generated by nitric oxide probably play a major role in the pathogenesis of lung cancer. However, it remains to be clarified whether the oxygen-derived oxidants, that is the ROS, are directly implicated in the pathogenesis of lung cancer in patients with COPD. In addition, in these patients, it would be necessary to identify which types of protein are modified by ROS and determine the loss of functionality (biological significance). It would also be necessary to investigate changes in DNA, which are crucially important in view of their possible implication in the progression from mutagenesis to neoplastic disease.

A better understanding of the molecular mechanisms implicated in the development of lung cancer in patients with mild or moderate COPD is essential for efforts to

improve quality of life and prolong survival. In the future, the exact identification of these mechanisms may help in the development of locally and/or systemically administered therapeutic strategies for patients with COPD that might be able to prevent or delay the appearance of lung cancer in these patients. The aim of this editorial has been to draw attention to an extremely important clinical situation with a direct impact on patients with COPD, especially those with not particularly advanced disease, whose quality of life is affected and prognosis is poor when diagnosed with lung cancer. This editorial also hopes to encourage suitably designed studies that would help investigate in detail the mechanisms potentially involved in carcinogenesis in bronchial and lung cells of patients with COPD.

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