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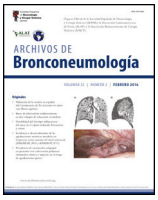

Letter to the Editor

Is an Early Diagnosis of COPD Clinically Useful?

¿Es clínicamente útil un diagnóstico temprano de EPOC?

Dear Editor,

An early diagnosis of a disease among people who feel well, reducing future morbidity and mortality, is important in many chronic diseases, especially in malignancy. An early diagnosis should benefit patients. However, even in such disorders, an early diagnosis can turn indolent pathologies into illness and screening can result in an excess of diagnoses.[1] This is over-diagnosis, a growing problem in high-income countries. It can be considered when the treatment of the diagnosed conditions, sometimes indolent situations that would never cause patients harm, cannot improve patients' outcomes, exposing them to unnecessary risks and therefore being potentially harmful.[2,3] Chronic Obstructive Pulmonary Disease (COPD) represents one of the most significant health problems at international level. It is the only leading cause of death with rising mortality and morbidity. COPD is considered to be an underdiagnosed and undertreated disorder, especially in its mild and moderate degrees. Although the need for an early detection makes sense, when can an early diagnosis become an over-diagnosis?

Over-diagnosis and misdiagnosis represent two different concepts.[4] Over-diagnosis means identifying problems that were never going to cause harm.[3] It has two major causes: 'over-detection' and 'over-definition'. Misdiagnosis consists in giving a wrong diagnosis to a person who is really ill.[3] In primary health care, many COPD diagnoses are made without a spirometry confirmation, using inadequate algorithms and with difficulties establishing the correct differential diagnoses.[5]

Spirometry has an important role in the early diagnosis of COPD. In the early stages of the disease the clinical manifestations are inconstant, usually minor and not valued by patients. Symptoms are frequently accepted as normal or expected, attributed to smoking, and patients do not seek medical attention until the disease is more advanced and their symptoms are already compromising daily activities. Although we acknowledge that the early pathological changes in COPD are not captured by spirometry,[6] we do not currently have any marker to detect early onset of the airway disease, though, the use of spirometry, depending on the values of reference used, may be a cause of over-diagnosis, especially in the elderly.[7]

Some authors argue that pharmacological interventions in the early stages of COPD, when a faster disease progression is known to occur,[8,9] are of significant importance as they could delay its progression, like in many other chronic disorders. However, there is a wide range in FEV_1 decline in patients with COPD, and there is no tool to identify patients who would benefit from treatment to prevent the deterioration of respiratory function. Moreover, no markers of the disease are known to predict which patients with a recent onset of the disease will progress to a greater severity.[10] Until now, the presence of symptoms in mild COPD – a significantly different concept than early COPD – is the best predictor of acceleration in FEV_1 decline. Asymptomatic patients with mild airflow limitation do not present a faster decline in FEV_1 neither have worse quality of life than healthy individuals.[11] However, they frequently present mild unreported exacerbations that impact patients' health status, and can be related to a small excess of FEV_1 decline.

An early diagnosis of COPD in people who feel well requires a significant amount of time, effort and costs. The US preventive Services Task Force (USPSTF) did not find evidence that screening for COPD using spirometry in asymptomatic people improves health outcomes (health-related quality of life, morbidity or mortality), and four of five trials assessing the effects of screening in smoking cessation did not report significant differences in abstinence rates. Therefore, the USPSTF concludes with moderate certainty that screening for COPD in asymptomatic people has no net benefit.[12] Many other published guidelines also recommended against screening for COPD in asymptomatic patients. The major goals in the treatment of COPD are the reduction of symptoms and exacerbations, and improvement of exercise tolerance and health status. However, the evidence achieved by most of the published RCTs related to pharmacological therapy can be applied only to patients with a severe or a very severe disease, because they do not use asymptomatic participants. Moreover, adherence to inhaled medications in COPD patients is strongly related to symptoms and to the functional severity of the disease.[13] A good adherence profile is then not expectable in patients with early disease, or with mild COPD.

Lung cancer screening with low-dose computed tomography can be useful to improve early-stage detection, increasing resectability and survival. COPD and cigarette smoking are two known independent risk factors for lung cancer. Because of that, some authors argued that the early diagnosis of COPD in smokers can help to select candidates for lung cancer screening.[14] It is infrequent to see a normal spirometry in patients with lung cancer.[15] Calabrò et al. demonstrated that even a small reduction in FEV_1% is a significant predictor of increased risk for lung cancer. Airflow obstruction can be understood as a surrogate marker for carcinogenic damage of the airways,[16] and screening for lung cancer can be done using a decrease in FEV_1%. These could be an important argument to support the importance of an early diagnosis of COPD.

We need an early diagnosis with demonstrated benefits to the patients but, without an accurate knowledge on markers of the disease activity, mainly in the early stages of COPD, guiding therapy and helping to understand the different accelerated declines in lung function, an early diagnosis can turn out to be an over-diagnosis.

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The Lower Airway Microbiome and Lung Cancer☆

Microbioma de la vía aérea inferior y cáncer de pulmón

To the Editor,

In a recent editorial, Garrido-Martin and Paz-Ares[1] commented on the novel contributions of the study of the microbiome in lung cancer patients, mainly with regard to the interesting expectations associated with its manipulation and the potential effect on the therapeutic response. The editorial also mentions, albeit briefly, the possibility of identifying certain microorganisms that could be used as diagnostic or prognostic biomarkers in lung cancer. Several studies of the respiratory microbiome have suggested the existence of characteristic changes in bacterial populations of the airway in these patients.[2,3] Although there are some differences in the studies, *Granulicatella*, *Streptococcus*, and *Veillonella* have been found most often in respiratory samples from patients with lung cancer.[2,3] Our group has conducted a study using specimens obtained by protected brush sampling in the side of the tumor and in the same area of the contralateral lung of patients with lung cancer and in controls without malignant disease.[3] Mass sequencing of bacterial DNA showed that the microbiota of the lower airway was similar in the tumor area and in the equivalent segment of the contralateral lung, but different from the microbiota detected in patients without cancer. These differences, as pointed out by Garrido-Martin and Paz-Ares,[1] could have a potential application as diagnostic biomarkers. In our experience, the identification of *Enterococcus*, *Capnocytophaga* and *Actinomyces* had a diagnostic accuracy for malignancy of 70%, and *Microbispora* allowed cancer to be ruled out with an accuracy of 78%.[3]

Studies to identify microorganisms as biomarkers in these patients use different methods and generally include a relatively low number of patients; moreover, the results may also vary due to alterations in respiratory microbiomes in different regions of the world,[4] so it is not yet possible to draw clinical conclusions. However, the study of the respiratory microbioma is undoubtedly a novel approach in the study of the pathogenesis of various diseases and diagnostic possibilities, or as noted by Garrido-Martin and Paz-Ares,[1] a potential strategy for modifying the therapeutic response of lung cancer.

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