Imaging and molecular biomarkers: a novel approach to screen populations at risk of pulmonary fibrosis?

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LDCT lung cancer screening in smokers may detect subclinical COPD and pulmonary fibrosis

<http://ow.ly/zfOq304aWy5>

An estimated 90 million subjects in the USA have a history of smoking, and are therefore at risk of developing smoke-related lung diseases including lung cancer, chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis. An ageing population, the lack of effective diagnostic and therapeutic approaches, and the modest impact of smoking cessation strategies largely explain why chronic lower respiratory diseases are presently a leading cause of death in the US adult population [1]. In 2014, a US National Heart, Lung and Blood Institute task force concluded that effective primary and secondary prevention of chronic lung diseases will require focused efforts to determine risk factors and characterise early-stage disease in at-risk groups. Additionally, development of surrogate measures such as imaging and molecular biomarkers are required to support the design of randomised clinical trials to test chronic lung disease preventive strategies [2].

Recent population studies using low-dose helical computed chest tomography (LDCT) have demonstrated that current or former heavy smokers can potentially benefit from lung cancer screening by increasing detection of early-stage lung cancers [3]. A reduction in all-cause mortality and modest complications associated with LDCT led the United States Preventive Services Task Force (USPSTF) to recommend annual screening for lung cancer with LDCT in adults aged 55–80 years who have a 30-pack-year smoking history and currently smoke or have quit within the past 15 years [4]. The Centers for Medicare and Medicaid Services (CMS) evaluated this recommendation in February 2015, and determined there was sufficient evidence to add lung cancer screening counselling and LDCT as a preventive service benefit under the Medicare programme [5]. This joint recommendation of the USPSTF and CMS is both unprecedented and forward looking, providing broad access to LDCT screening to millions of asymptomatic ever-smokers at risk of developing lung cancer and other smoke-related parenchymal lung diseases in the USA.

Smoking also increases the risk of developing COPD. An estimated 14% of US adults between the ages of 40 and 79 years have COPD [6], a disease presently ranked as the third leading cause of death in the USA [1]. Although airflow obstruction has been the key measure used to define COPD, recent studies demonstrated that asymptomatic and symptomatic smokers have changes consistent with early-stage parenchymal lung disease despite the absence of airflow obstruction. These studies demonstrate that current smoking is associated with more respiratory symptoms, while former smokers have greater evidence for emphysema and gas trapping. Remarkably, this study suggests that an additional 35 million smokers in the USA may have unrecognised disease [7]. Unfortunately, despite accumulating evidence that

Received: Aug 23 2016 | Accepted: Aug 23 2016

Support statement: The author is supported by US National Institutes of Health (National Heart, Lung and Blood Institute) grants P01 HL114501 and RO1 HL15024. Funding information for this article has been deposited with the Open Funder Registry.

Conflict of interest: None declared.

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LDCT can detect COPD in asymptomatic individuals, in 2016, the USPSTF did not find evidence that early detection altered disease course or improved patient outcomes, and recommended against screening for COPD [8].

In this issue of the *European Respiratory Journal*, PODOLANCZUK *et al.* [9] present compelling evidence that imaging and molecular biomarkers could potentially enhance the detection of subclinical interstitial lung disease (ILD). The authors sought to examine whether a quantitative measure of lung attenuation is associated with features of subclinical lung injury and all-cause mortality. To address the question, investigators measured high-attenuation areas (HAAs) on cardiac CT scans of participants in the Multi-Ethnic Study of Atherosclerosis (MESA), a large cohort of community-dwelling adults where approximately half of participants were former or current smokers. The investigators found that HAAs were more frequent in participants who were female, Hispanic or Chinese, with higher body mass index, and who were never-smokers. HAAs were associated with decreased lung volumes, exercise capacity and CT measures of emphysema. Moreover, HAAs were associated with increases in peripheral blood concentrations of matrix metalloproteinase (MMP)-7 and interleukin (IL)-6, particularly in smokers. In a subset of MESA participants with long-term follow up, HAAs were associated with increased risk of subclinical ILD and all-cause mortality. Clearly, this is an important contribution to the field of preventive medicine, which confirms similar findings from prior studies and further supports the potential role of LDCT as a tool to detect early-stage parenchymal lung disease [10, 11].

Several aspects of this research study are noteworthy. Participants with HAAs followed over a median of 12 years had an increase in all-cause mortality. Although the cause of death is not presented, this is an unexpected finding as most HAAs are thought to represent early-stage radiological changes in subjects with subclinical ILD. It is possible that participants died from respiratory causes; however, it is highly unlikely that a majority of subjects died from progressive interstitial pneumonia as <1% of subjects had radiological evidence of an established idiopathic interstitial pneumonia, despite a decade of longitudinal follow-up. Additionally, HAAs were associated with increases in select biomarkers. Increased MMP-7 levels have been previously reported in subclinical ILD [12], while increased IL-6 levels have been reported in patients with acute lung injury, not in subjects with pulmonary fibrosis [13]. Finally, participants with HAAs were more likely to be female and never-smokers, characteristics that are less frequent in patients with pulmonary fibrosis. Taken together, these findings suggest that HAAs and other automated algorithms that measure increased lung density may detect alveolar injury patterns that do not lead to meaningful alveolar remodelling or fibrosis. Hence, the cause of death in these individuals could be respiratory failure presenting as acute respiratory distress syndrome, acute interstitial pneumonia or both. Additional studies are required to define further the respiratory and nonrespiratory causes of death in individuals with increased HAAs.

As previously stated, the USPSTF and CMS recommend offering LDCT screening to millions of ever-smokers in the USA. One could argue that screening for early-stage disease could increase detection of incident and prevalent subclinical ILD; however, the modest number of cases with pulmonary fibrosis documented by PODOLANCZUK *et al.* [9] does not suggest that long-term follow-up of subjects with HAAs led to increased detection of pulmonary fibrosis in a large cohort of community-dwelling adults. Additionally, in contrast to subjects with lung cancer, it is unclear if a diagnostic lung biopsy would change the outcome of patients with subclinical ILD. Confirming a diagnosis and implementing therapies will be challenging, particularly when one accounts for poor drug tolerance and cost associated with antifibrotic therapies. Therefore, it is not clear that screening for pulmonary fibrosis with LDCT can improve clinical outcomes. Perhaps focusing on groups at higher risk of developing pulmonary fibrosis and the implementation of molecular signatures to stratify subjects at higher risk for disease progression will prove to be clinically beneficial [14].

In summary, we anticipate that LDCT screening for lung cancer in smokers will lead to the detection of subclinical COPD and pulmonary fibrosis in millions of US subjects at risk of developing pulmonary fibrosis. Lung cancer, COPD and pulmonary fibrosis funding agencies and clinical research networks should consider developing collaborative studies to support cross-disciplinary research studies of smoke-related lung disease. A more comprehensive assessment of the overall impact of LDCT screening in improving clinical outcomes will encourage the USPSTF to revise evidence-based screening strategies for smoke-related lung diseases. Finally, although there is no evidence that LCDT screening will improve clinical outcomes of patients affected with parenchymal lung disease, clinicians should continue to provide smoking cessation counselling and consider close monitoring of patients with evidence of subclinical lung disease.

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