Air Pollution as a Risk Factor for Lung Cancer: Potential Mechanisms

To the Editor:

Given our active research in the areas of epidemiology and mechanisms of obstructive lung disease and how/why chronic obstructive pulmonary disease (COPD) and lung cancer fit as closely together as they do, we were particularly interested in the recent stimulating article by Huang and colleagues (1) and the accompanying editorial by Chistiani (2), published online on August 9, 2021. The tight focus of each article was a timely analysis of the powerful UK Biobank Cohort database indicating genetic- and air pollution–related risks for lung cancer, with some other relevant factors taken into account in the analyses.

We were interested that neither article mentions COPD because there is evidence for this being a major causative link to lung cancer in smokers, which remains after accounting for the risk associated with smoking *per se*. This may well be related to the well-described underlying small airway remodeling pathology in smokers, with fibrotic narrowing/obliteration of small airways that leads to airway obstruction (3). Furthermore, there is increasing evidence for the specific linkage process between smoking, COPD, and lung cancer being a pathway though a cascade of reactive oxygen species activating the airway epithelium, leading to basal (stem) cell genetic reprogramming. This then leads to growth-factor production, strategic kinase, and transcription factor mobilization and ultimately to a final common mechanism of epithelial–mesenchymal transition (EMT). EMT is associated with myofibroblast proliferation and secondary excessive and abnormal matrix protein production with airway wall thickening (4). EMT is recognized as a vital, common part of malignancy pathogenesis across a swathe of epithelial cancers and thus is a mechanistically plausible etiological link between COPD and lung cancer development (3).

It is known that occupational and general air pollution gives rise to chronic fixed airflow obstruction with modulation of these effects by antioxidant gene polymorphisms (5). In view of this background, we would be very interested to know if Huang and colleagues (1) in their studies of this large United Kingdom population database have been able to explicitly integrate obstructive lung function spirometric abnormalities into their analysis, looking specifically for mediation or interactions by airway obstruction in the apparent air pollution effect on lung cancer. We believe that if it is possible within the UK Biobank data set, such an analysis could help inform and/or confirm potentially core relationships between environmental air pollution exposures, airway pathology, and the etiology of lung cancer in this globally relevant context of air pollution. ■

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Reply to Ward *et al.*

From the Authors:

We read the response letter by Ward and colleagues to our manuscript (1), and the accompanying editorial by Christiani (2),

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