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Epithelial–Mesenchymal Plasticity as a Potential Common Link between Lung Disease and Increased Risk of Lung Cancer

To the Editor:

We congratulate Choi and colleagues for their thought-provoking population cohort study showing that (non–cystic fibrosis) bronchiectasis increases the risk of lung cancer, independent of smoking status; risk of cancer was higher for people with bronchiectasis than without bronchiectasis (1). The authors highlight the growing recognition that chronic obstructive pulmonary disease (COPD) increases the risk of lung cancer, regardless of smoking status (2, 3).

Choi and colleagues cite our study of 986 patients with bronchiectasis across four European centers, which showed that numerous multisystem comorbidities often occur in people with bronchiectasis; COPD was prevalent, but gastroesophageal reflux disease was the most frequent comorbidity (4). The authors propose that in COPD and bronchiectasis, chronic inflammation is the common element in the development of lung cancer. We would like to highlight the potential role of epithelial–mesenchymal transition (EMT) and airway remodeling.

We suggest that EMT is a likely culprit, and oxidant damage secondary to inflammation may be a mediator. In EMT, epithelial cells lose organized cell-to-cell adhesion, apical basal polarity, and their epithelial proteome, gaining functional mesenchymal characteristics including migration and invasion, with degradation of underlying basement membrane and production of extracellular matrix components (5). EMT plays key roles in malignancy across many epithelial cancers and is recognized to occur as a spectrum of states, including "partial" EMT (2, 3, 5).

The role of EMT in lung disease has been very actively debated, and the term "epithelial–mesenchymal plasticity" (EMP) has been a helpful compromise. Thus, a range of pleiotropic oxidant injuries from cigarette smoke to air pollution, and quite possibly (infective) bronchiectasis independent of smoking, converge to bidirectional pathways of phenotypic epithelial dysregulation, with EMT as a final common risk factor for lung cancer (2, 3).

We first demonstrated that EMT/EMP is active in human airway disease in 2004 in lung allograft recipients, as part of the development of bronchiolitis obliterans syndrome (BOS) in chronic lung allograft dysfunction (2). The development of BOS involves airway epithelial injury from a number of causes, including infection and reflux-associated microaspiration, with neutrophilic airway inflammation consistently documented internationally. Bronchiectasis and bronchial wall thickening are commonly described in BOS, as in COPD, and lung cancer has a high incidence in both. We have also reported that even in smokers without COPD, EMT/EMP is active in airway epithelial basal cells (2, 3), though more marked in COPD (2, 3). Furthermore, about 30% of people with COPD from a primary care population have airway wall abnormalities classifiable as bronchiectasis, and a strong predictor of exacerbations in COPD is a patient history of symptomatic reflux, again emphasizing the commonalities in these airway conditions with high cancer risk.

In smokers we have shown that EMT/EMP in large airways is characterized by reticular basement membrane hypervascularity. This is a recognized characteristic of type III EMT (5), which we have also shown to be active at the peripheral leading edge of epithelium-derived non–small cell lung cancer tumors (6). EMT is a signal for an airway microenvironment favorable to the development of lung cancer (6).

We wonder whether Choi and colleagues may have further data to allow consideration of these potential interrelationships in bronchiectasis; for example, is chronic airflow limitation or gastroesophageal reflux associated? Such interactions may inform more tailored therapeutic interventions. For example, there is growing evidence that inhaled corticosteroid protects against lung cancer risk in COPD, and drugs that more specifically target EMT are being actively developed, at least in oncology (2, 3), and deserve to be trialed more widely in lung conditions in which EMT seems to play a critical role. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Reply: Epithelial–Mesenchymal Plasticity as a Potential Common Link between Lung Disease and Increased Risk of Lung Cancer

From the Authors:

We would like to thank Professor Ward and colleagues for reading and providing valuable comments on our study investigating the association between noncystic fibrosis bronchiectasis and lung cancer risk (1). Our findings indicated that participants with bronchiectasis have a higher risk of incident lung cancer compared with those without bronchiectasis, regardless of smoking status. We explained that chronic inflammation in bronchiectasis, as in chronic obstructive pulmonary disease (COPD), which is now recognized as a risk of lung cancer, may be a potential mechanism for lung cancer development (2).

Professor Ward and colleagues suggested epithelial–mesenchymal transition (EMT) as a culprit in lung cancer development in bronchiectasis. EMT is the gradual transformation of basal epithelial cells into mesenchymal-like cells (3). During the process, subepithelial reticular basement membrane fragmentation and hypervascularity develop, and the epithelial cells lose their characteristics and functionality. EMT is known to be involved in the tissue remodeling in COPD and lung cancer progression (3, 4). In this context, we agree with their suggestion that EMT can be a key mediator between chronic inflammation and lung cancer development in airway conditions with high cancer risk, including COPD and bronchiectasis.

As mentioned by Professor Ward and colleagues, chronic airflow limitation and gastroesophageal reflux disease (GERD) are significant comorbid conditions that influence the severity of chronic airway inflammation in bronchiectasis (5). Consequently, these factors may interact with bronchiectasis. Unfortunately, because of the absence of pulmonary function measurement data in our dataset, we could not analyze the impact of chronic airflow limitation (defined as forced expiratory volume in 1 second/forced vital capacity less than 0.7). However, we evaluated the impact of GERD on the association between bronchiectasis and lung cancer development using our prevalent cohorts. GERD was defined as at least one claim under the ICD (International Statistical Classification of Diseases and Related Health Problems), 10th Revision, code K21, within the preceding year before health screening. Stratified analysis revealed no significant interaction between the presence of GERD and bronchiectasis and the risk of developing lung cancer (P for interaction in Model 3 = 0.29). In addition, compared with that of participants without bronchiectasis or GERD, the risk of lung cancer was significantly increased in participants with GERD alone (adjusted hazard ratio [HR] in Model 3, 1.08; 95% confidence interval [CI], 1.04–1.11), those with bronchiectasis alone (adjusted HR, 1.24; 95% CI, 1.15–1.34), and those with both bronchiectasis and GERD (adjusted HR, 1.24; 95% CI, 1.12–1.38) (Table 1).

Although GERD is associated with the severity and progression of bronchiectasis, our results showed no significant synergistic effect of GERD and bronchiectasis on the risk of incident lung cancer. Considering that GERD can aggravate airway inflammation in bronchiectasis, which may induce an

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