



## Complex Relationship between Bronchiectasis and Lung Cancer

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Lung cancer is the leading cause of cancer-related deaths worldwide in both men and women (1). Tobacco smoking is known to be the strongest etiological factor for lung carcinogenesis, and the cumulative amount of smoking exposure in pack-years is the main factor for identifying high-risk individuals for developing lung cancer and possibly benefit from lung cancer screening (2, 3). Factors such as genetic susceptibility, occupational exposures, air pollution, and previous respiratory diseases also act independently or together with smoking as risk factors for lung cancer (4). Comorbid medical conditions such as chronic obstructive pulmonary disease (COPD), idiopathic pulmonary fibrosis, and a history of pulmonary tuberculosis infection are reported to increase the risk of lung cancer. In addition, a prior diagnosis of COPD (PLCOM<sub>2012</sub> model) or pneumonia (Liverpool Lung Project risk model) is a risk factor in validated multivariable risk-prediction models of lung cancer used to identify high-risk individuals (5, 6).

For patients with COPD, chronic inflammation causing repeated airway injury and high cell turnover rates likely plays a key role in lung carcinogenesis. Similarly, among the hypotheses suggested for the relationship between previous lung infection

and lung cancer, transition from the infection-engendered inflammatory dysplasia to cancer is an appealing supposition (7). Given this possible relationship between lung inflammation and lung cancer, noncystic bronchiectasis may be considered as a risk factor for lung cancer. Adult noncystic fibrosis bronchiectasis is a multicomponent chronic airway disease characterized by abnormal, permanent dilatation of the bronchi, accompanied by chronic systemic inflammation (8). Accumulating evidence suggests that patients with bronchiectasis are at risk of developing other comorbidities linked to systemic inflammation (9).

Although previous studies have reported a positive association between bronchiectasis and the risk of developing lung cancer, the possible mechanisms and the role of bronchiectasis-associated inflammation on lung carcinogenesis have not been well documented (10). Moreover, when evaluating the relationship between bronchiectasis and lung cancer, conditions and risk factors known to be associated with both bronchiectasis and lung cancer must be considered. Patients with bronchiectasis can be regarded as having a “double hit” because many might already have an underlying disorder that led to the development of bronchiectasis and potentially increase the risk of developing lung cancer. For example, patients with bronchiectasis associated with COPD or prior pulmonary infection could be at increased risk of lung cancer owing to the synergistic effects of smoking and airway inflammation (11).

In this issue of *Annals ATS*, Choi and colleagues (pp. 1551–1560) presented a nationwide study from South Korea describing the association between bronchiectasis and lung cancer risk, with adjustments and subgroup analyses by smoking intensity and comorbid COPD (12). The authors evaluated 3,858,422 (65,305 with underlying bronchiectasis and 3,793,117 without bronchiectasis) individuals who participated in the National Health Screening Program in 2009, with follow-up data up to

December 2018. The incidence of lung cancer was 2.099 per 1,000 person-years in the bronchiectasis group, compared with 0.742 per 1,000 person-years in those without, showing an elevated risk of lung cancer in the former (adjusted hazard ratio [HR], 1.28; 95% confidence interval [CI], 1.17–1.41 for never smokers and adjusted HR, 1.26; 95% CI, 1.10–1.44 for ever smokers). Although statistically significant, the incidence hazard ratios are generally lower compared with a previous large cohort study in Taiwan by Chung and colleagues that analyzed the risk of lung cancer in 53,755 newly hospitalized patients with bronchiectasis in contrast to a matched cohort of 215,020 individuals without bronchiectasis (13). This study reported a higher incidence of lung cancer in those with bronchiectasis than in the comparison cohort (4.58 vs. 2.02 per 1,000 person-years) and an increased risk of lung cancer in the individuals with underlying bronchiectasis (adjusted HR, 2.36; 95% CI, 2.19–2.55).

An important observation from the study by Choi and colleagues is that, when further stratified by the presence of underlying COPD, bronchiectasis was significantly associated with a higher risk of lung cancer in participants without COPD (adjusted HR, 1.19; 95% CI, 1.09–1.31), but the association in those with underlying COPD was not significant (adjusted HR, 1.06; 95% CI, 0.97–1.16). Although those with both bronchiectasis and COPD had a higher risk of developing lung cancer than those with neither (adjusted HR, 1.43; 95% CI, 1.31–1.56), the risk was attenuated in those with bronchiectasis only and without COPD (adjusted HR, 1.21; 95% CI, 1.10–1.32). Previous studies, including large-scale prospective cohorts, have widely reported the association between bronchiectasis and COPD. In bronchiectasis cohorts, COPD is reported to be a common comorbidity (approximately 20%) and is associated with a more severe disease course (9, 14). Similarly, Choi and colleagues reported that participants with bronchiectasis

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were more likely to have COPD than those without (32.9% vs. 4.5%) (12). Considering that COPD is a representative smoking-related disease and the well-established association between both COPD and smoking with the risk of lung cancer, evaluating the association between bronchiectasis and lung cancer in those with COPD becomes more complex. Therefore, the insignificant association of bronchiectasis and lung cancer shown in those with underlying COPD by Choi and colleagues warrants cautious interpretation, and further studies addressing their study's limitations are needed.

The major limitation of the study from Choi and colleagues is its inability to provide detailed information on the etiology and severity of both bronchiectasis and COPD. Noncystic bronchiectasis itself is a heterogeneous multicomponent disease with numerous etiologies and various extents and severities (15). Some etiologies and comorbid conditions, such as mycobacterial infection, pneumonia, and autoimmune diseases, might be associated with elevated lung cancer

risk, independent from bronchiectasis, or affect lung cancer development in patients with bronchiectasis. For patients with COPD, factors associated with a higher risk of developing lung cancer have been previously identified. A predictive risk scoring system including age, body mass index, smoking pack-years, and emphysema was developed, noting that a more severe disease is associated with a higher risk of lung cancer in patients with COPD (the COPD-LUCSS) (16). Determining risk factors and predictive scores can be useful in identifying patients who may benefit from lung cancer screening, which can be implemented into clinical practice. For bronchiectasis, McDonnell and colleagues recently developed the Bronchiectasis Etiology Comorbidity Index (BACI) from a European multicenter cohort analysis to identify comorbidities associated with the risk of mortality in patients with bronchiectasis (9). This study showed that bronchiectasis is positively associated with malignancies, including lung cancer, and these malignancies increase mortality risk in patients with bronchiectasis. In particular,

comorbid malignancies have the highest weight in the BACI (9). However, data on factors associated with a higher risk of developing lung cancer in patients with bronchiectasis remains limited. Future research with detailed information on the characteristics and comorbid conditions of patients with bronchiectasis is needed.

The worldwide burden of lung cancer remains significant, projected to rise during the coming years. Especially, in the era of lung cancer screening, identifying risk factors other than smoking is crucial to identify those who would benefit most from screening programs. Bronchiectasis, a heterogeneous disease that contributes to a considerable healthcare burden, is potentially associated with a higher risk of lung cancer development. Future studies should focus on more concrete evidence from cohorts with detailed clinical information and on identifying the major cause(s) of lung cancer in patients with bronchiectasis. ■

**Author disclosures** are available with the text of this article at [www.atsjournals.org](http://www.atsjournals.org).

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