

# Low diffusing capacity, emphysema, or pulmonary fibrosis: who is truly pulling the lung cancer strings?

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Ozeki *et al.* reported that patients with low carbon monoxide diffusing capacity of the lung (DLCO) values had lung adenocarcinoma with aggressive histopathological features (1). This correlation remained significant despite adjustment for potentially confounding variables such as age, smoking status, tumor size, and forced expiratory volume at 1 s. Thus, the observation suggests a theoretical concept that increased damage to the underlying lung can promote the carcinogenesis of aggressive lung cancer.

This paper raises further questions regarding what the low DLCO values truly represent. Are low DLCO values solely a sign of lung damage? Or do they represent other coexisting lung diseases such as emphysema or pulmonary fibrosis? Does damage of the underlying lung sequentially promote the aggressiveness of the lung cancer? Or do both lung cancer and damaged lung simultaneously result from a shared pathogenesis pathway?

## Lung diseases with low DLCO: emphysema, fibrosis, and CPFE

DLCO values represent the ability of the lung to transfer gas from the inhaled air into the blood stream and acts as a surrogate marker of the extent of lung damage (1). DLCO values may decrease because of several clinical conditions including emphysema, interstitial lung diseases, or pulmonary fibrosis (2). Thus, impaired DLCO values in lung cancer patients may suggest not only lung damage

but also the possibility of a co-existing comorbidity such as chronic obstructive pulmonary disease (COPD) or idiopathic pulmonary fibrosis (IPF).

COPD is characterized by airway obstruction on spirometry or emphysematous changes on computed tomography (CT) images. It is a well-known risk factor for lung cancer, and the incidence of lung cancer increases with worsening of the airway obstruction (3). Although squamous cell carcinoma is the most prevalent histology in COPD-related lung cancer, the presence of emphysema is also a risk factor of lung adenocarcinoma (4). In contrast to squamous cell carcinoma, adenocarcinoma tends to develop in areas with less emphysema. In addition, coexistence of COPD in adenocarcinoma is associated with less aggressive features, i.e., high percentage of lepidic tumors, low percent of solid tumors, and low proliferation rate by Ki-67 (5).

Pulmonary fibrosis is also known to increase the risk of lung cancer. Lung cancer in patients with IPF is inclined to develop in the honeycomb areas (6). This is similar in patients with combined pulmonary fibrosis and emphysema (CPFE), in whom lung cancer is prone to arise in areas with fibrotic change and dysplastic epithelium (7). Lung cancer in CPFE patients is associated with high tumor grade, high stage, and poor outcome.

In conclusion, emphysema, fibrosis, and CPFE are lung diseases associated with both impaired DLCO and increased risk of lung cancer. These comorbidities may confound the impact of DLCO on the carcinogenesis of

lung cancer. Thus, each of these comorbidities should be carefully assessed for their relation to the occurrence of lung cancer. Previous studies have underscored the association between lung cancer and underlying lung diseases, and several potential pathogenesis pathways have been suggested to explain this correlation.

### Damaged lung and cancer: a sequential of simultaneous relationship?

A damaged lung and cancer may form a part of multistage carcinogenesis. In other words, the underlying lung generates a field cancerization effect that may sequentially lead to lung cancer, among other consequences. Chronic inflammation caused by emphysema or fibrosis can result in epithelial cell injury, high cell turnover rates, and propagation of DNA errors, thereby promoting carcinogenesis (8). In particular, low DLCO may facilitate oxygen deprivation and increase the expression of hypoxia-inducible factors (HIFs). HIF expression is associated with tumor aggressiveness and metastasis in lung cancer (9). Hypoxia is also known to have extensive crosstalk with signaling pathways linked to inflammation (10).

In contrast, a common pathogenic pathway, such as that of genetic susceptibility, could be the overlapping cause for both the lung cancer and the underlying lung disease. For example, a genetically aberrant inflammatory-repair response to smoking or impaired immune-surveillance may contribute to the pathogenesis of both COPD and lung cancer (11). Similarly, pulmonary fibrosis and lung cancer share the common features of epigenetic and genetic changes, altered response to regulatory signals, abnormal expression of microRNAs, and activation of specific signaling pathways, which can be attributed to the causes of both fibrotic change and carcinogenesis (12).

### Further research

In conclusion, the paper by Ozeki and colleagues prompts further interpretation, research, and clinical application of DLCO for lung cancer management (1). Additional analysis of HIF expression can contribute toward the better understanding of the underlying molecular mechanism between low DLCO values and high tumor aggressiveness. In addition, as the role of driver mutation in lung adenocarcinoma is of great clinical importance, it would be of interest to evaluate the *EGFR* and *KRAS* mutation status in comparison with histopathology. We expect

that DLCO values may become an additional tool for improved and efficient selection of patients at high-risk for lung cancer and who should thus undergo lung cancer screening.

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### Footnote

*Conflicts of Interest:* The authors have no conflict of interest to declare.

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