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Tuberculosis, Chronic Obstructive Lung Disease, and Lung Cancer: The Holey Upper Lobe Trinity?

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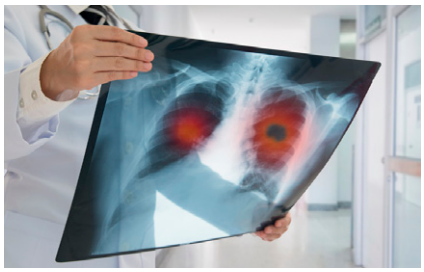

Tuberculosis (TB) research has traditionally focused on diagnostics and therapy for acute infections. TB diagnosis remains difficult, but several new diagnostics have been developed in recent years with higher sensitivity and specificity for diagnosis (1, 2). In addition, many advances have been made in the treatment of TB with promising high-efficacy treatment regimens of shorter duration. Treatment that used to take up to 9 months can now potentially be as short as 4 months (3). With better living conditions, improved nutrition, and the improvements in diagnosis and treatment of TB, more people are surviving TB. In 2019, 86% of people treated with first-line therapy were successfully treated for TB (4). As more people survive TB, long-term complications are increasingly recognized (5).

The potential complications after treated TB are numerous. They include chronic respiratory symptoms, post-tuberculous lung disease, and increased risk for specific lung diseases such as chronic obstructive pulmonary disease (COPD) (6), which in turn increase the risk for subsequent bouts of TB (7). Prior pulmonary TB is a known risk factor for the development of lung cancer (8). COPD, in addition to being associated with increased risk for TB, is a strong risk factor for development of lung cancer regardless of smoking status (9). As TB is associated with increased risk for both COPD and lung cancer, and COPD is associated with increased risk for lung cancer, the question is whether TB works synergistically with COPD, thereby further enhancing the risk for subsequent lung cancer.

In this issue of *AnnalsATS*, Park and colleagues (pp. 640–648) evaluated whether a history of pulmonary TB is associated with increased risk of lung cancer in people with COPD (10). Using a large national cohort with longitudinal follow-up, they evaluated the risk of lung cancer after TB in both smokers and never-smokers with COPD. To evaluate the effect of COPD on the risk of lung cancer after pulmonary TB, they matched 1:3 individuals with and without COPD. The authors found that a history of pulmonary TB was associated with a 1.23-fold increased risk of lung cancer among people with COPD. Among the participants without COPD, there was no association of prior pulmonary TB with risk of lung cancer in this cohort.

In this cohort, a large proportion of participants were never-smokers, with only 31.7% of those with no prior TB and 44.2% of those with a history of TB being ever-smokers (past and current). The proportion of never-smokers with COPD diagnoses was substantial, at approximately 66%. The authors thus performed a subanalysis in never-smokers to assess whether the relationship of prior pulmonary TB with lung cancer persists in those who do not have

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the confounder of smoking. Notably, the association of lung cancer with prior pulmonary TB was stronger in never-smokers than in ever-smokers with COPD. In these subanalyses among those without COPD, there again was no relationship of pulmonary TB with lung cancer in either smokers or never-smokers.

The results of this study suggest a potential synergism of pulmonary TB and COPD in increasing risk for lung cancer. The large cohort allowed for the comparison of the effect of pulmonary TB in people with and without COPD. The authors were also able to evaluate both smokers and never-smokers, thus mitigating the potential confounding effect of smoking on the development of lung cancer. The authors postulate that the weakened relationship of pulmonary TB with lung cancer in smokers may be owing to the dominant effect of smoking in lung cancer development, which may have "overridden" the effect of pulmonary TB on lung cancer development. As TB and COPD each increase the risk for the other condition, and both commonly lead to chronic inflammation and affect upper lung lobes (the most common site of lung cancers), the results suggest an interaction of pulmonary TB and COPD in the development of lung cancer.

Important limitations in this study include the definition of COPD and TB. COPD was defined by the presence of a COPD *International Classifications of Disease, Tenth Revision* code and prescription of COPD medication at least twice a year. Use of existing electronic health record diagnoses without spirometry (the gold standard for the diagnosis of COPD) may have led to both misdiagnosis and underdiagnosis of COPD (11, 12). Significantly, the authors defined TB as having "active or inactive" TB on the basis of chest X-ray (CXR). This may have led to misclassification of participants as having TB, because CXR has high sensitivity but poor specificity for the diagnosis of pulmonary TB (13), making CXR excellent for TB screening but not a diagnostic test. In addition, the analyses did not include pack-years or years of smoking in smoking status. Furthermore, the smoking status was not time updated throughout or at the end of the study (a duration of up to 13 years for some participants), raising the possibility of misclassification of never-smoking status.

A surprising finding is that TB was not associated with an increased risk for lung cancer in those without COPD in this cohort. Reasons for this lack of association are unclear, given that TB has previously been shown to be a risk factor for lung cancer. The findings in the present study suggest that the link between TB and increased risk of lung cancer is found only in those with COPD. Interpreting these findings is limited by the potential misclassification in the diagnoses of TB and COPD, as discussed above. Because of these limitations, and because *1*) the association of TB and risk for lung cancer was stronger in never-smokers with COPD diagnoses and *2*) given the high proportion of never-smokers among those with COPD, an additional question is raised: is the chronic lung disease in these patients actually COPD, or something different, such as another form of post-tuberculous lung disease that may differentially increase the risk for lung cancer? Additional studies are needed with more detailed characterization of lung disease and diagnoses of TB to answer these questions.

What are the scientific implications of the findings? Overall, the findings are intriguing; the predominant involvement of the upper lobes with TB and COPD—and frequent occurrence of lung cancer in the upper lobes—raises questions about the local inflammatory and immunologic milieu that may predispose to carcinogenesis. In addition, TB is not the only pulmonary infection linked with lung cancer risk (14–17), raising questions as to the role of microbes in this process. As this is an electronic database study, the authors are unable to determine whether participants had COPD first with subsequent TB or vice versa. Future studies outlining the timeline and associated risk factors for subsequent lung cancer would be helpful in informing risk stratification, as well as additional translational and bench studies to gain insights into mechanisms.

Future work should also consider the role of human immunodeficiency virus (HIV) when assessing the relationship between pulmonary TB and risk for lung cancer. The authors do not address HIV coinfection, a potential confounder, as HIV infection increases the risk for TB and predisposes to both COPD (18) and lung cancer (19, 20) in smokers and nonsmokers. In addition, HIV infection is associated with chronic inflammation, potentially further enhancing the relationship of TB and COPD with lung cancer development. Studies that include people living with HIV and tease out the effect of HIV/TB coinfection in people with COPD are necessary to assess additional risk in this vulnerable population.

Finally, what are the clinical implications of this study? The authors suggest that patients with COPD with a history of pulmonary TB might benefit from periodic screening or assessment for lung cancer even if they are nonsmokers. Current lung cancer screening guidelines focus on tobacco use and years of smoking (21) and do not endorse screening in nonsmokers or those with COPD and other potential risks for lung cancer if they do not otherwise meet eligiblity criteria. By screening heavy smokers who meet current eligibility criteria per U.S. Preventative Services Task Force recommendations, we are missing other individuals who are nonetheless at risk of lung cancer. However, it is unclear if the overall benefits would exceed the harms for lung cancer screening in other populations, such as patients with prior TB. Furthermore, screening in those with pulmonary infections and subsequent radiographic abnormalities may lead to unnecessary angst and interventions, a substantial increase in the number of CT scans, and an increased cost of lung cancer screening programs. Larger, more generalizable studies evaluating the true risk of lung cancer with pulmonary TB and potentially other pulmonary infections in people with COPD may inform future modeling studies and guide updates in lung cancer screening guidelines. Thus, although no formal screening recommendations can be made at this time, increased awareness of the risk for lung cancer in survivors of pulmonary TB, particularly never-smokers with COPD, is warranted. ■

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