The Course of Lung Function in Middle-aged Heavy Smokers: Incidence and Time to Early Onset of Chronic Obstructive Pulmonary Disease

To the Editor:

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. Cigarette smoking is an important risk factor for COPD; however, not all heavy smokers develop COPD. In fact, the majority of smokers do not develop airflow limitation consistent with COPD, whereas 25–35% appear to be susceptible, deteriorating into clinical COPD at a young age (1, 2). COPD severity and progression in patients younger than 50 years is similar to that of patients older than 65 years (3), suggesting that the process begins much earlier in life in subjects at risk for the disease. In support of this concept, Lange and colleagues showed that the combination of low baseline lung function (LF) and rapid LF decline, as defined by mean annual loss of 40 ml FEV_1 or more (rapid decline [RD]), results in "impending" development of COPD compared with subjects having only one or neither of the conditions (4). We tested the hypothesis that middle-aged and heavy smokers with low LF and rapid LF decline trajectory have a high hazard ratio to develop COPD at an earlier time than smokers with other LF trajectories.

Since 2001, the Lovelace Smokers Cohort (LSC), a community-based cohort of volunteers, has been recruiting heavy current and former smokers (≥10 pack-years) with ages ranging from 40 to 75 years. These smokers are either at risk for development of COPD or have already acquired the disease. Details regarding the LSC have been published previously (5, 6). The LSC captures questionnaire, demographic, and pre- and postbronchodilator spirometry data. Visits occur at 18-month intervals, and LF change can be characterized over time. In this study, we sought to investigate the incidence and factors involved in the development of spirometric Global Initiative for Obstructive Lung Disease stage II COPD in smokers at risk (32.4 mean pack-years) aged 40 to 50 years and followed for a mean period of 4 years. COPD in subjects younger than 50 years of age with 10 pack-years or more was recently termed early COPD (7)

Study participants were selected on the basis of their LF trajectories, grouped according to the combination of baseline LF and LF decline status. From the initial cohort of 2,273 LSC volunteers, 1,553 subjects had a minimum of two visits used to determine LF change, as previously reported (8). From these subjects, we selected those aged 40–50 years at baseline ($n = 685$). These subjects were grouped into tertiles of baseline LF, as well as into tertiles of annual rate of FEV_1 change between baseline and most recent spirometry measurements. Subjects falling into the middle tertile of either baseline LF or LF change were excluded. Therefore, the four comparison groups comprised participants with high or low baseline LF, each with no decline (ND) or RD in LF.

All groups were similar in age, sex, socioeconomic status (educational attainment), pack-years, and current smoking status. Subjects in the low LF/RD group were slightly older than those in the other groups, and were more likely to demonstrate bronchodilator reversibility, but no differences were observed with respect to exposure to pollutants, parental smoking, comorbidities, or medication use.

Participants in the low LF/RD group had the highest prevalence of baseline COPD and the lowest FEV_1/FVC ratio (Table 1). The proportion of subjects with a modified Medical Research Council dyspnea score ≥2 was the highest in the low LF/RD group. St. George's Respiratory Questionnaire total scores and symptom, activity, and impact subscale scores were highest, and 36-item Short Form Questionnaire scores lowest (indicating worse health status), in the low LF/RD group. The proportion of New Mexico Hispanics was higher in the high baseline LF groups, in keeping with other studies that have reported LF protection for this ethnic group (5). However, excluding Hispanics from these analyses did not change any of the demographic or clinical results shown in Table 1. Most important, incident COPD was significantly higher in subjects with low LF/RD, and the mean number of days to incident COPD was 0.33–0.5 times the interval for incident COPD seen in the other groups. After adjusting for age, sex, body mass index, socioeconomic status, pack-years, and current smoking status, the relative risk for incident COPD was significantly higher, with a hazard ratio of 36.6 (95% confidence interval, 4.1–320.9) in subjects with low LF/RD compared with subjects with high LF/ND. The relative risk for the other groups was not significantly increased.

This study shows that among middle-aged heavy smokers, those with baseline low LF and RD are at the highest risk of developing COPD within 4 years of observation. Although the pathobiological pathways leading to COPD may already be initiated in those without disease at baseline, the clinical manifestations may not be visible at this stage. However, for those with incident COPD, the risk of developing COPD was extremely high, and the days to incident COPD was a third of the days for patients with high LF/ND (Figure 1). RD status can be determined with two spirometry readings spaced 12 months or more apart. Acknowledging that smoking cessation is of primary importance, these results have clinical relevance, in that subjects with baseline LF of FEV_1 75% predicted had a 40% chance of being categorized in the RD category and, therefore, would benefit from serial screening spirometry measurements to determine LF trajectory. Furthermore, because subjects in the LF/RD group have the highest percentage of subjects with bronchodilator reversibility, LF measurements should be performed pre- and postbronchodilator administration to decrease variability of measurement. Self-reported history of doctor-diagnosed asthma was similar for all groups (Table 1). Low LF and rapid decline of 40 ml/year may help detect those smokers at highest risk for incident COPD and identify a subgroup of smokers that might benefit the most from intensive secondary preventative measures, such as smoking cessation strategies or avoidance of secondhand smoke exposure. Because the LSC is not representative of the general population, research efforts are needed to replicate this study in other cohorts. In addition, samples from subjects developing early COPD are needed to identify the pathobiological mechanisms responsible for baseline low LF and RD among younger individuals. ■

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Table 1. Comparison of Selected Lung Function Trajectory Groups among Young Smokers (40–50 yr of Age) in the Lovelace Smokers' Cohort ($N = 222$)

Characteristics	ND		RD		*P* Value
	High LF (*n* = 40)	Low LF (*n* = 70)	High LF (*n* = 68)	Low LF (*n* = 44)	
Age, yr	44.6 ± 3.2	45.4 ± 3.9	44.8 ± 3.1	46.7 ± 3.2	**0.03**
Male	10 (25)	21 (30)	18 (26.5)	7 (15.9)	0.26
Hispanic	15 (37.5)	21 (30)	16 (23.5)	6 (13.6)	**0.01**
BMI, kg/m^2	27.6 ± 6.3	30.6 ± 8	26.9 ± 5.2	27.2 ± 6.4	0.13
Education, ⩾HS	23 (57.5)	47 (67.1)	54 (79.4)	23 (52.3)	0.92
Current smoker	30 (75)	56 (80)	45 (66.2)	34 (77.3)	0.56
Pack-year	30.2 ± 13.7	34.5 ± 15.8	28 ± 10.2	36.9 ± 16.4	0.34
Exposure to fumes	14 (35)	19 (27.5)	19 (27.9)	14 (32.6)	0.87
Exposure to dust	6 (15)	6 (8.7)	5 (7.4)	9 (20.9)	0.48
Wood smoke exposure	10 (25.6)	20 (29)	19 (28.4)	16 (37.2)	0.31
Follow-up, yr	4.1 ± 2.1	4.2 ± 2.4	4.3 ± 2.5	3.3 ± 2.3	0.19
Visits, *n*	4 ± 1.4	4 ± 1.5	4 ± 1.5	3 ± 1.3	0.06
FEV_1, L	3.5 ± 0.7	2.5 ± 0.5	3.5 ± 0.7	2.3 ± 0.5	**0.001**
FVC, L	4.3 ± 0.9	3.4 ± 0.7	4.4 ± 0.9	3.3 ± 0.8	0.05
FEV_1/FVC × 100	80.7 ± 3.2	73.7 ± 9.7	79.9 ± 4.8	70.5 ± 10.4	**0.001**
FEV_1% predicted	106.2 ± 6.1	76 ± 10.4	108.5 ± 7.4	74.9 ± 12.7	**0.002**
FVC% predicted	106.1 ± 6.2	83.1 ± 11.7	109.5 ± 8.9	85.3 ± 11.4	0.09
Bronchodilator reversibility	0 (0)	1 (1.4)	2 (2.9)	8 (18.2)	**0.001**
TLC, L	5.7 ± 0.5	6 ± 1.4	6 ± 1.2	6 ± 1.3	0.72
D_{LCO}, ml/min/mm Hg	30.5 ± 2.9	23.2 ± 7	25.8 ± 6.6	23.3 ± 11.7	0.54
Baseline COPD	0 (0)	19 (27.1)	2 (2.9)	18 (40.9)	**0.01**
Incident COPD	2 (5)	3 (4.3)	3 (4.4)	10 (22.7)	**0.01**
Days to Inc. COPD	1,502 ± 775	1,101 ± 1021	1,506 ± 936	525 ± 618	**0.001**
Age at Inc. COPD, yr	52 ± 7.1	49 ± 5	49.3 ± 5.5	49.5 ± 2.8	0.69
FEV% diff.	−4.7 ± 3	−13.3 ± 15.8	8.9 ± 3.2	13.4 ± 10.3	**<0.0001**
FVC% diff.	−5.5 ± 4.2	−10.9 ± 10	5.8 ± 4.7	5.1 ± 9.8	**<0.0001**
Ann. absolute FVC diff.	0.1	0.1	−0.1	−0.1	**<0.0001**
Ann. decline rate, L	0.06 ± 0.1	0.1 ± 0.1	−0.09 ± 0.1	−0.1 ± 0.1	**<0.0001**
Chron. bronchitis	10 (25)	29 (41.4)	25 (36.8)	18 (40.9)	0.29
mMRC score ⩾ 2	10 (25)	29 (41.4)	19 (27.9)	29 (67.4)	**0.004**
SGRQ total	16.3 ± 17.6	24.2 ± 17.3	18.2 ± 15.8	28.8 ± 20.7	**0.03**
SF-36 total	118.5 ± 20.5	111.4 ± 21.3	117.3 ± 17.2	104.8 ± 20.5	**0.04**
History of asthma	7 (17.5)	19 (27.5)	15 (22.1)	8 (18.6)	0.79

Definition of abbreviations: Ann. = annual; BMI = body mass index; Chron. bronchitis = chronic bronchitis (self-reported cough and phlegm for at least 3 mo over the course of 2 consecutive years); COPD = chronic obstructive pulmonary disease; diff. = difference; HS = high school; Inc. = incident; LF = lung function; mMRC = modified Medical Research Council Dyspnea Questionnaire; ND = no decline; RD = rapid decline; SF-36 = 36-Item Short Form Questionnaire; SGRQ = St. George's Respiratory Questionnaire.

Data are shown as *n* (%) or mean ± SD. Unless otherwise indicated, all variables shown are at baseline. Significant *P* values appear in bold. The *P* values shown are based on the Jonckheere Terpstra test for categorical variables and multivariate analysis of variance for continuous variables.

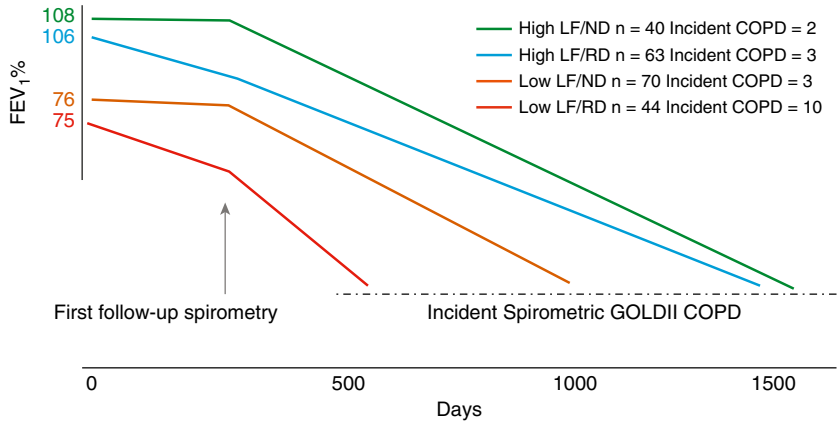

Figure 1. Days to incident chronic obstructive pulmonary disease (COPD). Lung function (LF) as expressed by the FEV_1% of predicted is determined at baseline, and the rate of decline by at least one postbronchodilator spirometry obtained 18 months apart. Incident COPD occurred earlier in subjects with low lung function at baseline, and the hazard ratio was higher in subjects with low LF at baseline and rapid rate of decline. *See* text for more details. GOLD = Global Initiative for Obstructive Lung Disease; ND = no decline; RD = rapid decline.

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Implications of Tuberculosis Reactivation after Immune Checkpoint Inhibition

To the Editor:

Treatment of malignant disease with immune checkpoint inhibitors is emerging as a transformative approach. However, tuberculosis (TB) reactivation associated with these agents is being increasingly reported (Table 1). We describe a further case of TB associated with anti–PD-1 (programmed cell death-1) immunotherapy and perform immunohistochemical analysis of lung biopsies from patients with standard or anti–PD-1–associated TB. We discuss the potential underlying mechanisms and implications for clinical practice and research.

TB Associated with Pembrolizumab, an Antibody to PD-1

A 62-year-old woman was diagnosed with ocular melanoma, which was excised. Three years later, metastatic disease developed and immune checkpoint inhibition therapy was commenced, initially with ipilimumab, an anti–CTLA-4 (cytotoxic T-lymphocyte–associated antigen 4) antibody, and then with pembrolizumab, a humanized monoclonal antibody against PD-1. The disease was stable for 2 years, but then blood liver biochemical markers became abnormal and a lung lesion was noted on computed tomographic scanning. Liver function abnormalities persisted despite immunosuppression, and so a liver biopsy was performed, which showed a single granuloma. Biopsy of the cavitating apical lung lesion showed necrotizing granulomatous inflammation, and bronchial washings cultured *Mycobacterium tuberculosis* (*Mtb*). Antituberculosis treatment was initiated, which led to clinical improvement, normalization of liver function tests, and regression of the lung lesion. Therefore, the unifying diagnosis was disseminated TB associated with immune checkpoint inhibition. However, this clinical occurrence runs counter to the current disease paradigm, which proposes that active TB results from a deficient host immune response (1).

Therefore, we performed immunohistochemical analysis of TB lung lesions in the context of a normal immune response (six cases) and the lung biopsy of this case. Immunostaining was performed for PD-L1 (programmed cell death ligand-1), CD8, and PD-1. In normal TB granulomas, PD-L1 is highly expressed, while PD-1 colocalizes with CD8, demonstrating that immune checkpoint ligands and receptors are coexpressed (Figure 1A). In the context of anti–PD-1 therapy, a similar picture of PD-L1 and CD8 expression within granulomas is observed, while PD-1 immunoreactivity appears reduced (Figure 1B). Therefore, the immune checkpoint inhibition pathway is active within TB granulomas.

Potential Mechanisms of Immune Checkpoint Inhibition Causing TB Reactivation

PD-1 is a cell surface receptor that binds ligands PD-L1 and PD-L2 and has important functions in the maintenance of immune tolerance. PD-1 inhibitors are therefore used to reverse tolerance to tumors and improve immune-mediated control of malignant disease (2). The use of these checkpoint inhibitors has been transformative to the field (2). In TB, progression from latent to active infection is regarded as a failure of the immune response, as demonstrated by the increased incidence of TB in the context of HIV infection or after anti–tumor necrosis factor treatment for inflammatory conditions (1). Consequently, it seems highly counterintuitive that PD-1 blockade should also cause activation of TB, as by this paradigm anti–PD-1 therapy should improve host control of TB. Indeed, PD-1 inhibition has been suggested as a host-directed therapy in TB (3), on the basis that the PD-1 pathway may inhibit an effective host response.

Mechanistically, these observations suggest that immune checkpoint signaling is important to conserve immune homeostasis within TB granulomas and prevent excessive inflammation that may lead to tissue destruction and cavitation (4). In terms of the cellular events leading to TB, depletion of *Mtb*-responsive T cells

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