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Prediction of Acute Respiratory Disease in Current and Former Smokers With and Without COPD

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BACKGROUND: The risk factors for acute episodes of respiratory disease in current and former smokers who do not have COPD are unknown.

METHODS: Eight thousand two hundred forty-six non-Hispanic white and black current and former smokers in the Genetic Epidemiology of COPD (COPDGene) cohort had longitudinal follow-up (LFU) every 6 months to determine acute respiratory episodes requiring antibiotics or systemic corticosteroids, an ED visit, or hospitalization. Negative binomial regression was used to determine the factors associated with acute respiratory episodes. A Cox proportional hazards model was used to determine adjusted hazard ratios (HRs) for time to first episode and an acute episode of respiratory disease risk score.

RESULTS: At enrollment, 4,442 subjects did not have COPD, 658 had mild COPD, and 3,146 had moderate or worse COPD. Nine thousand three hundred three acute episodes of respiratory disease and 2,707 hospitalizations were reported in LFU (3,044 acute episodes of respiratory disease and 827 hospitalizations in those without COPD). Major predictors included acute episodes of respiratory disease in year prior to enrollment (HR, 1.20; 95% CI, 1.15-1.24 per exacerbation), airflow obstruction (HR, 0.94; 95% CI, 0.91-0.96 per 10% change in % predicted FEV_1), and poor health-related quality of life (HR, 1.07; 95% CI, 1.06-1.08 for each 4-unit increase in St. George's Respiratory Questionnaire score). Risks were similar for those with and without COPD.

CONCLUSIONS: Although acute episode of respiratory disease rates are higher in subjects with COPD, risk factors are similar, and at a population level, there are more episodes in smokers without COPD.

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ABBREVIATIONS: COPDGene = Genetic Epidemiology of COPD; ECLIPSE = Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; GERD = gastroesophageal reflux disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HR = hazard ratio; LFU = longitudinal follow-up; SGRQ = St. George's Respiratory Questionnaire

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More than 100 million people have a smoking history in the United States, and 20% of the population currently smokes.[1] Many of these people experience episodes of acute respiratory disease characterized by increased or new shortness of breath, cough, and/or change in sputum quantity or quality.[2] The cost of treating these acute episodes exceeds $30 billion per year.[3] The current medical knowledge and literature are confusing because these acute episodes of respiratory disease have multiple terminologies such as acute bronchitis,[4] exacerbations of chronic bronchitis,[5] and acute exacerbations of COPD,[6] despite the fact that the pathophysiology (bacterial and viral infections) and treatment (corticosteroids and antibiotics) are similar. Furthermore, most studies of acute episodes of respiratory disease in current and former smokers include only patients with significant airflow limitation (ie, moderate or more severe COPD) despite population surveys indicating that most current and former smokers do not meet the spirometric criteria for COPD.[1] This large understudied group may pose a significant, underrecognized health-care burden, and there is an unmet need to define and quantitate their risk of acute episodes of respiratory disease.

Most current knowledge of acute episodes of respiratory disease in current and former smokers comes from studies of patients with COPD. These episodes are referred to as acute exacerbations of COPD and are associated with decreased quality of life,[7,8] increased lung function decline,[9] and higher mortality.[10-12] Multiple cross-sectional studies have identified common factors associated with acute exacerbations of COPD such as severe airflow obstruction, poor health-related quality of life,[13] gastroesophageal reflux,[14] and chronic bronchitis.[15] Age, sex, BMI, a history of cardiovascular disease, theophylline use, and a lack of influenza vaccine are also independent risk factors.[16-18] Most of these cross-sectional studies did not include smokers without COPD and few contained a large number of underrepresented populations (eg, blacks).

The Genetic Epidemiology of COPD (COPDGene) study has multiple unique features that make it ideal for studying these unmet needs: (1) it is one of the largest prospective studies of subjects with COPD and also those who are at risk of, but do not meet the spirometric criteria for, COPD; (2) it includes a large number of blacks; and (3) its subjects have been well characterized clinically and by quantitative high-resolution chest CT scan.

Materials and Methods

Study Population

The COPDGene study consists of 10,300 subjects at 21 centers across the United States.[19] COPDGene was approved by the institutional review board at each participating center, and all subjects provided written informed consent. The current analysis was approved by the National Jewish Health Institutional Review Board (AS-1887). Subjects were enrolled from January 2008 to April 2011. At the time of enrollment, all subjects were 45 to 80 years old, had a history of smoking for at least 10 pack-years, and had not had an acute respiratory exacerbation for at least 30 days prior to enrollment. Additional characteristics of the study population and study methodology have been described previously.[15,19,20] Although originally designed as a single-visit cross-sectional study, the COPDGene cohort was converted into a longitudinal study in its second year. Of the 10,300 subjects originally enrolled, 8,246 participated in a longitudinal follow-up (LFU), defined as at least one follow-up contact at least 6 months after initial enrollment. LFU was conducted every 6 months by telephonic, web-based inquiry as described previously.[21] A research coordinator contacted those subjects who did not complete a telephonic or web-based follow-up.

Clinical Definitions

COPD was defined as a postbronchodilator FEV_1/FVC ratio < 0.70. COPD was further classified as I to IV based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines,[22] where GOLD I: $FEV_1/FVC < 0.7$ and $FEV_1 \geq 80\%$; GOLD II: $FEV_1/FVC < 0.7$ and $50\% \leq FEV_1$, 80% predicted; GOLD III: $FEV_1/FVC < 0.7$ and $30\% \leq FEV_1$, 50% predicted; GOLD IV: $FEV_1/FVC < 0.7$ and $FEV_1 < 30\%$ predicted. Current or ex-smokers at risk of COPD but without spirometric evidence of airflow obstruction ($FEV_1/FVC \geq 0.70$) were classified as control subjects (formerly, GOLD 0). Subjects with $FEV_1/FVC \geq 0.70$ and $FEV_1 < 80\%$ were considered unclassified (GOLD U).[23] Emphysema was quantified by the percent of lung voxels < -950 Hounsfield units on the inspiratory images of CT scan. Gas trapping was quantified by the percent of lung voxels < -856 Hounsfield units on the expiratory images. The pulmonary artery was measured in the tubular portion and the aorta was measured at the arch,

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