Respiratory Medicine (2014) 108, 491–499

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

The clinical impact of non-obstructive chronic bronchitis in current and former smokers☆

Carlos H. Martinez [a,*], Victor Kim [b], Yahong Chen [c], Ella A. Kazerooni [d], Susan Murray [e], Gerard J. Criner [b], Jeffrey L. Curtis [a,f], Elizabeth A. Regan [g], Emily Wan [h], Craig P. Hersh [h], Edwin K. Silverman [h], James D. Crapo [g], Fernando J. Martinez [a,1], MeiLan K. Han [a,1], The COPDGene Investigators

[a] *Pulmonary & Critical Care Division, University of Michigan Health System, Ann Arbor, MI, USA*
[b] *Division of Pulmonary and Critical Care, Temple University School of Medicine, Philadelphia, PA, USA*
[c] *Respiratory Department, Peking University Third Hospital, Beijing, China*
[d] *Department of Radiology, University of Michigan, Ann Arbor, MI, USA*
[e] *School of Public Health, University of Michigan, Ann Arbor, MI, USA*
[f] *Medicine Service, VA Healthcare System, Ann Arbor, MI, USA*
[g] *Department of Medicine, National Jewish Medical and Research Center, Denver, CO, USA*
[h] *Channing Division of Network Medicine and Pulmonary and Critical Care Division, Brigham and Women's Hospital, Boston, MA, USA*

Received 15 May 2013; accepted 7 November 2013
Available online 15 November 2013

KEYWORDS
Cough;
Quality of life;
Gastroesophageal reflux;
Occupational exposure;
GERD;
Tobacco

Summary
Background: As the clinical significance of chronic bronchitis among smokers without airflow obstruction is unclear, we sought to determine morbidity associated with this disorder.
Methods: We examined subjects from the COPDGene study and compared those with $FEV_1/FVC \geq 0.70$, no diagnosis of asthma and chronic bronchitis as defined as a history of cough and phlegm production for ≥3 months/year for ≥2 years (NCB) to non-obstructed subjects without chronic bronchitis (CB-). Multivariate analysis was used to determine factors associated with and impact of NCB.
Results: We identified 597 NCB and 4283 CB- subjects. NCB participants were younger (55.4 vs. 57.2 years, $p < 0.001$) with greater tobacco exposure (42.9 vs. 37.8 pack-years, $p < 0.001$) and more

☆ **Prior abstract presentation**: Presented as an abstract at the American Thoracic Society International Conference, San Francisco 2012.

* Corresponding author. Division of Pulmonary and Critical Care Medicine, University of Michigan Health System, 3916 Taubman Center, Box 0360, 1500 E. Medical Center Drive, Ann Arbor, MI 48109-5360, USA. Tel.: +1 734 763 2540; fax: +1 734 936 5048.
E-mail address: carlosma@umich.edu (C.H. Martinez).

[1] Co-senior authors.

http://dx.doi.org/10.1016/j.rmed.2013.11.003

often current smokers; more frequently reported occupational exposure to fumes (52.8% vs. 42.2%, $p < 0.001$), dust for ≥1 year (55.3% vs. 42.0%, $p < 0.001$) and were less likely to be currently working. NCB subjects demonstrated worse quality-of-life (SGRQ 35.6 vs. 15.1, $p < 0.001$) and exercise capacity (walk distance 415 vs. 449 m, $p < 0.001$) and more frequently reported respiratory "flare-ups" requiring treatment with antibiotics or steroids (0.30 vs. 0.10 annual events/subject, $p < 0.001$) prior to enrollment and during follow-up (0.34 vs. 0.16 annual events/subject, $p < 0.001$). In multivariate analysis, current smoking, GERD, sleep apnea and occupational exposures were significantly associated with NCB.

Conclusions: While longitudinal data will be needed to determine whether NCB progresses to COPD, NCB patients have poorer quality-of-life, exercise capacity and frequent respiratory events. Beyond smoking cessation interventions, further research is warranted to determine the benefit of other therapeutics in this population.

Clinical Trials Registration # NCT00608764 (http://clinicaltrials.gov/show/NCT00608764).

Link to study protocol: http://www.copdgene.org/sites/default/files/COPDGeneProtocol-5-0_06-19-2009.pdf.

Abbreviations

NCB	non-obstructive chronic bronchitis
CB-	chronic bronchitis symptoms absent
FEV_1	forced expiratory volume in the first second
FVC	forced vital capacity
SGRQ	Saint-George's Respiratory Questionnaire
GERD	gastro-esophageal reflux disease
COPD	chronic obstructive pulmonary disease
QOL	quality-of-life
GOLD	Global Initiative for Obstructive Lung Disease
NHANES	National Health and Nutrition Examination Survey
SF-36	Short Form Health Survey, 36-item
SF-36 PCS	physical component score of the SF-36
SF-36 MCS	mental component score of the SF-36
BMI	body mass index
MMRC	Modified Medical Research Council Dyspnea Score
6MWD	six-minute walking distance
OR	odds ratio
OSA	obstructive sleep apnea
MCID	minimal clinically important difference

Introduction

The pathways involved in the development of COPD and lung cancer after exposure to tobacco smoke involve airway inflammation, oxidative damage and impaired repair [1,2]. Chronic cough and phlegm in smokers have also been correlated with pathologic, functional, and molecular signatures of chronic inflammation [3—5]. Cross-sectional studies have validated the existence of a chronic bronchitis phenotype among smokers with established airway obstruction [6,7]. While several population based studies have reported poorer quality-of-life (QOL), more frequent infections and accelerated lung function decline [8—11] in these patients, the impact of chronic bronchitis in those without airflow obstruction is less clear. Epidemiologic studies suggest chronic bronchitis is a risk factor for incidental airflow obstruction, but mainly within subjects younger than 50 years of age [8]. Therefore is possible that in some patients, non-obstructive chronic bronchitis (NCB) is an early presentation of COPD whereas in others it may be a distinct disorder. In the absence of airflow obstruction, however, this group of patients is typically overlooked with respect to assessment and the development of treatments. Using participants from the COPDGene study who were all current or former smokers without airflow obstruction and without history of asthma, in a cross-sectional design and with additional follow-up for two years, we hypothesized that when compared to those without chronic bronchitis symptoms, subjects with non-obstructive chronic bronchitis (NCB) would have worse quality of life, poorer exercise tolerance and more frequent respiratory events at baseline and during follow-up.

Methods

Patient selection

Briefly, the COPDGene Study (http://www.copdgene.org/), described in detail previously [12] is a NHLBI-funded multicenter investigation of the genetic epidemiology of smoking-related lung disease, which recently completed inclusion of the baseline cohort of more than 10,000 participants (Clinical Trials Registration # NCT00608764). Subjects were enrolled between January 2008 and June 2011. Inclusion criteria include ability to give informed consent; age 45—80 years; cigarette smoking ≥10 pack years; and willingness to undergo study-related testing including spirometry and a chest CT scan. For our analysis, all subjects