COPD in the never-smoker

David M. Mannino
Kathryn Marie McGonigle

Available at: https://works.bepress.com/david_mannino/120/
PCCU - Lesson 23

COPD in the Never-Smoker

By David M. Mannino, MD, FCCP; and Kathryn Marie McGonigle

Objectives

1. Identify never-smokers as an important subset of the COPD population.
2. Discuss the relationship between asthma and COPD.
3. Understand the genetic components of COPD.
4. Identify occupational risk factors for COPD.
5. Discuss prevention methods for COPD in the never-smoker.

Key words

asthma; COPD; genetics; never-smoker; occupation; risk factors

Abbreviations

DALY = disability-adjusted life-year; GOLD = Global Initiative for Chronic Obstructive Lung Disease; IL = interleukin; NHANES III = Third National Health and Nutrition Examination Survey; TNF-a = tumor necrosis factor-a

Definition of COPD

Several different definitions have traditionally existed for COPD.\textsuperscript{1,2} The recently published and widely accepted definition from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) has classified COPD as "a disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually both progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases."\textsuperscript{3} This definition, which depends on physiologic changes rather than a clinical diagnosis, makes it much easier to classify never-smokers as having COPD. The subtypes of COPD (asthmatic, bronchitic, and emphysematous) may have both different etiologies and outcomes, along with different treatment strategies.

Airflow limitation is the slowing of expiratory airflow as measured by spirometry, with a persistently low FEV\textsubscript{1} and a low FEV\textsubscript{1}/FVC ratio despite treatment. The GOLD definition for airflow limitation is an FEV\textsubscript{1}/FVC ratio of < 70%. Airflow limitation reversibility can be spontaneous, in response to an inhaled bronchodilator, or in response to oral or inhaled corticosteroids. The GOLD definition of COPD classifies reversibility as an FEV\textsubscript{1} increase of 200 mL and 12% improvement above baseline FEV\textsubscript{1}.3 While COPD has been closely linked to cigarette smoking in the developed world, smoking has never been part of any definition of COPD, although it typically enters into clinicians' decision making.

Epidemiology of COPD

In 2000, an estimated 10 million US adults reported physician-diagnosed COPD.\textsuperscript{4} Data from the Third National Health and Nutrition Examination Survey (NHANES III), however, estimate that among 11 million US adults with evidence of low lung function, < 40% reported a diagnosis of COPD or asthma, suggesting that
COPD is underdiagnosed.\(^5\) In 2000, COPD was responsible for 8 million physician-office and hospital outpatient visits, 1.5 million emergency department visits, 726,000 hospitalizations, and 119,000 deaths. The most dramatic change over the 21-year period analyzed in the Centers for Disease Control report was the increase in the COPD death rate for women, from 20.1 per 100,000 in 1980 to 56.7 per 100,000 in 2000, compared with the more modest increase in the death rate for men, from 73.0 per 100,000 in 1980 to 82.6 per 100,000 in 2000.\(^4\) COPD is a costly disease, with estimated direct medical costs in 1993 of $14.7 billion.\(^6\) The estimated indirect costs related to morbidity (loss of work time and productivity) and premature mortality represent an additional $9.2 billion, for a total of $23.9 billion. When the $12.6 billion in indirect and direct medical costs attributable to asthma are added to this, the total cost of obstructive lung disease in the United States is $36.1 billion. Another manifestation of the importance of COPD is its effect on the burden of disease in population determined using disability-adjusted life-years (DALYs).\(^7\) In 1996, COPD was estimated to be the eighth leading cause of DALYs among men and the seventh leading cause of DALYs among women.\(^7\) Worldwide, COPD is expected to move up from the 12th leading cause of DALYs in 1990 to the fifth leading cause in 2020.\(^8\)

Smoking is the primary risk factor for the development and progression of COPD; however, < 25% of smokers develop COPD\(^9\) and about 15% of COPD-related mortality occurs in never-smokers, suggesting that other factors are important.\(^10\) Several pathways have been proposed for the pathogenesis of COPD: reduced lung growth during childhood to young adulthood (from birth to 15 years in women and from birth to 25 years in men); a premature decline when lung function should be stable during young adulthood (age 15 to 35 years); or accelerated decline in lung function after the age of 35 years.\(^11\) Identified factors other than smoking that are important in COPD development and progression include asthma and bronchial responsiveness,\(^12\) occupation,\(^13\) genetic factors,\(^9\) air pollution,\(^14\) sex,\(^15,16\) socioeconomic status,\(^17\) nutrition,\(^18\) and childhood exposures.\(^19\) Understanding how these factors work together to cause diminished lung function in never-smokers may improve our understanding of and treatment options for COPD in general population. In addition, the majority of COPD in the developing world probably occurs in never-smokers.

### Epidemiology of COPD in the Never-Smoker

As noted above, 15 to 20% of the COPD in the US population occurs in never-smokers. In a report from the Third National Health and Nutrition Examination Survey (NHANES III) 3.0 % of never-smokers had evidence of low lung function (FEV\(_1\) < 80% predicted and FEV\(_1\)/FVC < 0.70).\(^5\) In that study, of the estimated 11.5 million adults with low lung function, 2.3 million (about 20%) had never smoked (Table 1). In NHANES III, reversibility testing was not done, so some people classified as having low lung function may have had asthma. Another recent study has shown that in COPD-related deaths in the United States in 1993, 17% occurred in never-smokers.\(^10\) In that study, a history of asthma was a strong risk factor for COPD-related mortality in the never-smoker (odds ratio, 13.9; 95% confidence interval, 6.09, 32.4).

### Table 1—COPD in Never-Smokers*

<table>
<thead>
<tr>
<th>Race/Sex</th>
<th>Population</th>
<th>Percentage With GOLD Stage 2 or 3 COPD</th>
<th>No. With GOLD Stage 2 or 3 COPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black/female</td>
<td>6,823,000</td>
<td>2.6</td>
<td>160,000</td>
</tr>
<tr>
<td>Black/male</td>
<td>3,771,000</td>
<td>4.8</td>
<td>116,000</td>
</tr>
<tr>
<td>White/female</td>
<td>41,120,000</td>
<td>3.1</td>
<td>1,396,000</td>
</tr>
<tr>
<td>White/male</td>
<td>26,010,000</td>
<td>3.3</td>
<td>680,000</td>
</tr>
<tr>
<td>Total</td>
<td>77,724,000</td>
<td>3.0</td>
<td>2,352,000</td>
</tr>
</tbody>
</table>

*Data from NHANES III.\(^5\)

### Pathogenesis of COPD in the Never-Smoker
Factors responsible for the development of COPD in the never-smoker are still being defined. The COPD model that has been applied in smokers (Fig 1) probably remains accurate in never-smokers. Because the "noxious particles and gases" stimulus (tobacco smoke in smokers) is much less in never-smokers, reviewing COPD in never-smokers may provide a better understanding of how the other modifying factors work together to cause in COPD. The role of intrinsic factors (asthma and bronchial responsiveness, genetics, sex, aging) and extrinsic factors (infections, air pollution, nutrition, occupational exposures, pediatric exposures) in the development and progression of COPD in the never-smoker will now be explored.

Figure 1. Pathogenesis of COPD. From GOLD.3

Intrinsic Factors in COPD Pathogenesis

Asthma and bronchial responsiveness. Asthma and COPD have traditionally been defined as separate diseases owing to their distinct pathogenesis and reversibility of airway obstruction, although in the GOLD definition of COPD, asthma with lung function impairment that is not fully reversible is a subtype of COPD. Asthma and allergy have been shown to be important factors in the pathogenesis of COPD.12,20 Other longitudinal studies, however, have shown that there are differences in survival and pulmonary function decline in subjects with decreased lung function at baseline who have asthma vs those without asthma, with survival being much better and lung function decline being less marked in the asthmatic patients.21

Although the symptoms in asthma and other subtypes of COPD can be similar, there are physiologic differences in the inflammatory processes leading to these conditions.3,11 The bronchitic subtype of COPD is primarily a neutrophilic inflammation, with increases in macrophages and CD8+ T lymphocytes and the inflammatory mediators tumor necrosis factor-a (TNF-a), interleukin-8 (IL-8), and leukotriene B4. Resultant epithelial squamous metaplasia, parenchymal destruction, glandular hyperplasia, and mucous metaplasia lead to airway narrowing, fibrosis, and permanent remodeling of the lung parenchyma and airways. Asthmatic inflammation comprises primarily eosinophils, CD4+ T lymphocytes, and mast cells, with leukotriene D4, IL-4, and IL-5 as the main inflammatory mediators. Inflammation results in a fragile epithelium, a thickened basement membrane, glandular hyperplasia, and mucous metaplasia (Table 2).

Table 2—Characteristics of Inflammation in COPD and Asthma*

<table>
<thead>
<tr>
<th></th>
<th>COPD</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cells</td>
<td>Neutrophils</td>
<td>Eosinophils</td>
</tr>
</tbody>
</table>
Airway hyperresponsiveness, which is the bronchoconstrictive response to a nonspecific stimulus such as methacholine or cold air, is associated both with impaired growth of the lungs during childhood and hastened decline of lung function during adulthood. There is some evidence that there may be less airway responsiveness in patients with the bronchitic form of COPD compared with subjects who have asthma; whether this observation is related to airway caliber rather than bronchial responsiveness is unknown. The relationship between bronchodilator reversibility, bronchial responsiveness, and lung function decline is complex, with different studies showing conflicting results. Intuitively, a higher degree of reversibility suggests that less remodeling has occurred, suggesting that with appropriate interventions these patients might have better prognoses.

**Genetics.** Both asthma and COPD have genetic determinants, although only α1-antitrypsin deficiency (PiZZ) has been shown definitively to be a risk factor for the development of the emphysematous form of COPD. Even among subjects with severe deficiency, however, there is considerable variability in the degree of lung function impairment, suggesting that other environmental or genetic factors are important in disease development and progression. Several different genetic factors probably contribute to the development of COPD in the never-smoker. Important determinants include mucociliary clearance rates, responses to hypoxia and hypercapnia, modulators of the pulmonary inflammatory response, antiproteases, modulators of cellular repair in the lung, enzymes that metabolize pulmonary toxicants, variability in proteolytic enzymes, and other unknown factors. In addition, factors that influence asthma prevalence, severity, and response to therapy may also be important. Table 3 lists candidate genes that have been investigated for both asthma and COPD. Currently, the only genes appearing on both lists are those for TNF-a and human leukocyte antigen.

### Table 3—Candidate Genes That Have Been Associated With COPD or Asthma/Atopy in Various Studies

<table>
<thead>
<tr>
<th>COPD</th>
<th>Asthma / Atopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>PiMZ α1-antitrypsin deficiency</td>
<td>TNF-a</td>
</tr>
<tr>
<td>TNF-a</td>
<td>Human leukocyte antigen</td>
</tr>
<tr>
<td>Microsomal epoxide hydrolase</td>
<td>Interleukin-4</td>
</tr>
<tr>
<td>Glutathione S-transferase</td>
<td>Interleukin-9</td>
</tr>
<tr>
<td>Heme oxygenase-1</td>
<td>β2-Adrenergic receptor</td>
</tr>
<tr>
<td>Taq-I polymorphism of α1-antitrypsin</td>
<td>5-Lipoxygenase</td>
</tr>
<tr>
<td>α1-Antichymotrypsin</td>
<td>High-affinity receptor for IgE (FceR1B)</td>
</tr>
<tr>
<td>Vitamin D binding protein</td>
<td>T cell receptor α/d</td>
</tr>
<tr>
<td>ABO blood group</td>
<td>Clara cell protein (CC16)</td>
</tr>
<tr>
<td>ABH secretor status</td>
<td></td>
</tr>
</tbody>
</table>
Sex. The role of sex in the development and progression of COPD is currently the subject of several studies. Recent data have shown that in 2000, more women than men in the United States reported that they had COPD, were hospitalized for COPD, and died from COPD. While much of this finding is probably related to smoking trends over time in women, it is also possible that hormonal or other factors, such as increased bronchial responsiveness or different patterns in usage of medical care, may also be important. Other data, however, show that similar proportions of men and women, stratified by smoking status, have evidence of airflow limitation. In developing countries, where cigarette smoking is typically less prevalent in women, increased rates of COPD have been found in women who use wood-burning stoves for heating and cooking. It is currently unclear whether women are more or less likely than men to develop COPD, given similar exposures.

Aging. Aging leads to a natural deterioration of many vital body functions, including lung function. Numerous studies have shown that lung function deteriorates with increasing age in both smoking and nonsmoking populations, although the decline is more rapid in smokers. Both asthma and the presence of respiratory symptoms have been shown to increase the FEV1 decline associated with aging. The specific factors leading to this deterioration are not well defined, but may be related to changes in the immune system, long-term exposures to pollutants, comorbid conditions, or other undefined factors.

### Extrinsic Factors in COPD Pathogenesis

**Occupational exposures.** Occupational exposures play an important role in COPD development and progression. Occupationally related COPD can occur in either the presence or the absence of agents known to induce occupational asthma, and it is useful to look at these exposure classifications separately.

More than 200 agents are known to cause asthma in the workplace; a partial list is shown in Table 4. Continued exposure to occupational asthmogens, such as plicatic acid, grain dust, cotton dust, or toluene diisocyanate, has been shown to result in irreversible airflow limitation. These exposures can be modified by other factors, such as genetics or smoking.

#### Table 4—Selected Occupational Agents Associated With Asthma and COPD

<table>
<thead>
<tr>
<th>Agent</th>
<th>Occupation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asthma</strong></td>
<td></td>
</tr>
<tr>
<td>Grain dust</td>
<td>Grain handling</td>
</tr>
<tr>
<td>Toluene diisocyanate</td>
<td>Foam manufacturing, plastics</td>
</tr>
<tr>
<td>Trimellitic anhydride</td>
<td>Plastics, epoxy resins</td>
</tr>
<tr>
<td>Platinum salts</td>
<td>Platinum refining</td>
</tr>
<tr>
<td>Western red cedar (plicatic acid)</td>
<td>Logging, lumber processing</td>
</tr>
<tr>
<td>Colophony</td>
<td>Electronics manufacturing</td>
</tr>
<tr>
<td>Natural latex</td>
<td>Health care</td>
</tr>
<tr>
<td>Pigeons</td>
<td>Pigeon breeding</td>
</tr>
<tr>
<td>Crabs</td>
<td>Crab production/processing</td>
</tr>
<tr>
<td>Trypsin</td>
<td>Pharmaceutical processing</td>
</tr>
<tr>
<td>Bacillus subtilis</td>
<td>Detergent manufacturing</td>
</tr>
<tr>
<td><strong>COPD</strong></td>
<td></td>
</tr>
<tr>
<td>Cadmium</td>
<td>Metal processing</td>
</tr>
<tr>
<td>Coal dust</td>
<td>Mining</td>
</tr>
</tbody>
</table>
COPD can also occur with occupational exposures not associated with asthma development. Cadmium is unique in that it is the one occupational agent that causes emphysema. Other occupational exposures linked to the development of COPD include mineral dusts, welding fumes, chlorine gas, and, most recently, popcorn flavoring.

High-dose irritant exposures (i.e., fire smoke, chlorine gas) that cause a life-threatening acute pulmonary toxicity may result in reactive airways dysfunction syndrome or bronchiolitis obliterans.

Air pollution. Both outdoor and indoor air pollutants can cause exacerbations of existing lung disease. The primary outdoor air pollutants of interest include ozone, particulate matter, and sulfur dioxide; important indoor pollutants include environmental tobacco smoke, wood smoke, and nitrogen oxides.

Recent longitudinal studies have suggested an association between exposure to ozone, particulate matter, and sulfur dioxide and decreased lung function in a population of never-smokers. This effect was increased in subjects whose parents had a history of respiratory disease (asthma, bronchitis, emphysema, hay fever), suggesting an additional genetic influence.

Exposure to indoor air pollutants can frequently result in higher exposures than one would obtain from outdoor exposures. Tobacco smoke, wood smoke, and cooking fumes have all been associated with the development of COPD. As was demonstrated with outdoor exposures, indoor exposures also result in more COPD among people with genetic risk factors.

Pediatric exposures. Impaired lung function, poor lung growth in utero, and premature or accelerated declines in lung function during childhood can eventually lead to COPD or other respiratory diseases during adulthood. Important exposures associated with impaired lung growth in children include tobacco smoke exposure and lower respiratory infections.

Infections. Lower respiratory tract infections, during both childhood and adulthood, are implicated in the pathogenesis of COPD and have important roles in COPD exacerbation. The main etiologic agents of adult COPD-related infections include *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and *Staphylococcus aureus*. *Psuedomonas aeruginosa* has more recently been identified as a component in severe COPD cases. Adenovirus and other common respiratory viral pathogens are also found. It is not clear whether respiratory infections are more important in COPD development in those who have never smoked.

Nutrition. Nutritional factors are probably important in the development and progression of COPD. Antioxidants such as vitamin E, vitamin C, and N-acetylcysteine have been found to be beneficial in decreasing COPD exacerbations in some studies. Retinoid use has been associated with neoalveolarization. Vitamin C and flavonoids have been associated with improved lung function. Fish oils have been shown to be associated with better lung function. Poor nutritional status has also been implicated in accelerated disease decline. Weight loss, cachexia, and muscle weakness are associated with increased oxidative stress, increased TNF-α levels, and a worsened prognosis.

**Prevention and Intervention**

Although COPD is predominantly a disease of smokers, it does occur in never-smokers and former smokers. In that setting, the most important COPD intervention, smoking cessation, is not possible. A key part of intervening in these patients is early detection and treatment. Patients with asthma are at risk for developing...
COPD, and both monitoring of their lung function status and aggressive treatment of their underlying condition are merited. Eliminating occupational or avocational exposures that can worsen lung function is also critical. Finally, because of the strong familial component of COPD, evaluating children and siblings of never-smoking patients who develop COPD may provide opportunities for early intervention.

References


42. Wilson R. The role of infection in COPD. Chest 1998; 113(suppl):242S-248S


Copyright ©2003 American College of Chest Physicians