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Sex and race factors in early-onset COPD

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Abstract

Purpose of review—Unlike other major diseases, mortality for chronic obstructive pulmonary disease (COPD) continues to increase. In recent years, COPD has evolved to increasingly affect women, minorities, and individuals from low socioeconomic groups. In women and African-Americans, evidence exists supporting the earlier development of COPD after less lifetime smoking. This review highlights new information on racial and sex differences in COPD.

Recent findings—Sex and related hormonal changes affect T-cell phenotypes, immunity, and smoking-related metabolism of toxic intermediate metabolites. Alterations in the bronchoalveolar lavage proteome of women, but not of men, have allowed the differentiation of healthy female smokers from smokers with COPD. Sex significantly influences levels of inflammatory cytokines and correlates with different clinical and physiological parameters in female COPD patients. African-Americans with COPD are younger, smoke less, are more likely to currently smoke, and have worse health-related quality of life (QOL). African-Americans are more likely to report hospitalized exacerbations that impact QOL. African-Americans with COPD and asthma are nearly four times more likely to experience exacerbations.

Summary—There are sex-specific and race-related differences in the manifestation of COPD. These differences warrant further physiologic, biologic, and genetic investigations.

Keywords

African-American; chronic obstructive pulmonary disease; nicotine; sex

INTRODUCTION

Over recent decades, the vital statistics for chronic obstructive pulmonary disease (COPD) have significantly changed. From 1980 to 2000, concurrent with an increase in the prevalence of COPD in women, the estimated annual number of COPD hospitalizations for women increased by nearly 42% and COPD deaths for women approximately tripled [1]. In 2000, deaths for women with COPD exceeded deaths in men, a pivotal event [1]. Since that time, COPD prevalence has been higher for women in all age groups through age 74 years [2]. From 2007 to 2009, 7.4 million women had a diagnosis of COPD (6.1%) compared with 4.4 million men (4.1%) [2]. From 1999 to 2007, the trend in deaths due to COPD declined for men only. In 2007, COPD resulted in the death of 60 000 men (63.5/100 000) versus 65 000 deaths in women (46.8/100 000) [2]. These data are attributed to changing social norms

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Conflicts of interest:

There are no conflicts of interest.

and acceptance of smoking in women with increasing smoking rates for women beginning after 1930 [3]. However, not all smokers develop COPD and the development of COPD despite fewer cigarettes per lifetime suggests that women and others may have intrinsic susceptibility to COPD with predisposition to enhanced damage from tobacco smoke.

Similarly, although African-Americans have a lower prevalence of COPD in the United States, several reports have demonstrated that African-Americans develop COPD with less intense cumulative smoking and at younger ages. Chatila *et al.* [4] reported their experience in a single center study of 160 African-Americans and white patients who were referred for lung volume reduction surgery or lung transplantation. The African-American patients were younger at presentation and had lower cumulative tobacco smoke exposure, despite comparable lung function. In the National Emphysema Treatment Trial, a randomized comparison of standard therapy versus lung volume reduction surgery that was restricted to patients with severe emphysema, no differences were found in pulmonary function, gas exchange, or exercise tolerance, but the African-Americans were significantly younger, 63 ± 7 versus 67 ± 6 years, $P = 0.01$ and smoked less [5]. An analysis of risk factors for early-onset COPD in the COPDGene Study, defined as age less than 55 years and forced expiratory volume in 1 s (FEV₁) less than 50% predicted, reported female predominance (66%), a greater prevalence in African-Americans (42 versus 14%) and association with current smoking, asthma, maternal smoking, and maternal COPD [6]. Although it has been suggested that disparities in COPD are entirely explainable by socioeconomic factors [7], this explanation is insufficient.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND SEX

Sex differences in COPD manifested as symptoms, comorbidities, or in varying radiographic phenotypes obtained from volumetric CT scanning are increasingly recognized [8,9–11]. Risk factors for COPD include heritable factors (genes), exposure to inhaled particulates (cigarette smoking, biomass fuels from indoor cooking, and dusts), oxidative stress, infections, reduced lung growth and development, age, sex, and socioeconomic factors [12,13]. In women, evidence exists to support differential effects by sex with many of these factors. Silverman *et al.* [14] reported that female smokers who were first-degree relatives of individuals with severe COPD were more likely to exhibit significantly lower lung function in comparison to male relatives who smoked. Since that time, female patients with COPD have been reported to have shorter times to first COPD exacerbation, with higher exacerbation rates [9], and worse quality of life with increased anxiety and depression despite less impaired lung function [11]. Despite similar ages of smoking initiation and similar rates of smoking, women consume fewer cigarettes per day and have lower cotinine levels [15]. A recent systematic review of 11 population-based studies suggested greater susceptibility among women to develop COPD by demonstrating faster annual decline in FEV₁ percent predicted among smoking women compared with men [16]. Although causes of death are similar in men and women with COPD, women have been reported to experience more arrhythmias, cancer, ischemic heart disease, and renal failure with less hypertension, mental disorders, osteoporosis, and rheumatoid arthritis [10].

Sex hormones display complex influences on lung growth and development, airway hyper-responsiveness, detoxification of tobacco smoke, and in the manifestation of chronic lung diseases, such as the pubertal switch in asthma from a male-predominant to a female-predominant disease. Estrogen has the ability to induce differentiation and maturation of the lung. Estrogens may be involved in the production of cytokines, triggering a TH2 dominant immune response [17]. Menopause, which is age-related and associated with decline in estrogen and progesterone, is an important cause of accelerated alveolar loss. Estrogen receptor β is the predominant estrogen receptor in the lungs, and its stimulation by estradiol

causes proliferation of lung cancer cells. Estrogen receptor α is a ligand activator factor and its activation induces differentiation and maturation. The stimulation of these receptors in the lungs increases protein expression of cytochrome P450 (CYP) enzyme-related pathways. Female smokers have increased lung expression of CYP enzymes (CYP1A1 by 2.0-fold) compared with male smokers. Increased susceptibility to oxidant-mediated lung injury, supported by murine studies, may result from increased CYP expression related to increased estradiol levels without alteration of the second phase of enzymes necessary for metabolism of the approximately 4000 chemicals present in tobacco smoke [18*].

Several studies have shown that postmenopausal women who use hormone replacement therapy (estrogen and progesterone) experience less pulmonary function decline and less inflammation than older women who do not take exogenous hormones, including former smokers and never smokers. This is unrelated to lower rates of smoking or other health factors. Administration of estrogen plus progesterone, estrogen alone, or an estrogen-like compound to postmenopausal women increases forced vital capacity and FEV₁. Even in women aged 24–35 years, the use of an oral contraceptive containing estradiol and a progestin increases forced expiratory flow rates, especially flow rates at low lung volumes. These findings in younger women point to the alveolar maintaining effect, and, perhaps, an alveolar regenerating ability of ovarian hormones [19]. This may also suggest that hormone replacement therapy affects pulmonary function by reducing airway obstruction. Evidence is growing to indicate estrogen may delay the loss of and improve those lung functions that reflect maintenance of alveolar structure and, as a consequence, the number of alveolar attachments to small conducting airways [19]. The influence of sex hormones on sex disparities in airway diseases may find support in studies of cilia beat frequency in airway epithelium [20] and the effect of estrogen on airway smooth muscle [21] and epithelial nitric oxide production [22]. Some authors have posited estrogen receptors as a potential new therapeutic target.

Murine studies have suggested that adipokines are associated with inflammatory lung diseases. Leptin and adiponectin receptors are expressed in human lung tissue. Adiponectin, a proinflammatory cytokine, is inversely related to lung function in male patients with COPD [23]. Leptin, a pro-inflammatory adipokine that affects innate and adaptive immunity, is a protein product of the *ob* gene, with synthesis and secretion by white adipose tissue [23]. Systemic leptin may be increased in COPD patients, particularly in women [23]. Leptin, expressed in bronchial epithelial cells, type II pneumocytes, and macrophages, differentially increases TH1 cytokine production, suppresses TH2 cytokine production, and increases the release of vascular endothelial growth factor (VEGF) [23]. BMI-adjusted leptin may predict COPD prevalence in women, rises with COPD exacerbations, and may be associated with disease severity. In a study investigating sex-related differences in adipokines in relation to systemic inflammatory biomarkers in stable COPD patients and BMI-matched controls, COPD patients were characterized by systemic inflammation, and leptin secretion increased with increasing fat mass, especially in female COPD patients in whom leptin and C-reactive protein were significantly correlated [24]. Additionally, women with COPD had higher systemic leptin levels than female controls. Polymorphisms in leptin have been associated with lung function decline [23] and lower FEV₁ [25]. Despite the potential relationship of leptin with sex, inflammation, and lung function, these findings are preliminary, awaiting confirmatory studies with adequate power, sample size or longitudinal follow-up to adjust for the confounding effect of obesity or assess the impact of weight intervention or modulation of adipokines [23].

Metabolomic profiling of genome-wide association data is a strategy for exploring gene regulatory networks and molecular biology [26]. This body of literature has been criticized for lacking consideration of sex differences or stratification by sex. Few such studies have

been done investigating sex differences in COPD. de Torres *et al.* [27] reported a pilot study of sex differences in plasma biomarkers. Plasma levels of interleukin (IL)-6, IL-8, IL-16, matrix metalloproteinase 9, tumor necrosis factor- α , monocyte chemoattractant protein-1 (MCP-1), pulmonary and activation-regulated chemokine (PARC), and VEGF were measured in 152 stable COPD patients and 80 smokers (50% women). Sex was independently associated with IL-6, IL-16, and VEGF after adjustment for smoking history. In COPD patients, plasma levels of IL-6 and VEGF were higher in men, $P = 0.032$ and 0.02 , respectively. Plasma levels of IL-16 were higher in females, $P = 0.009$. In females, IL-16 correlated positively with BMI and VEGF negatively correlated with age and BODE index. In men, IL-6 correlated with diffusing capacity of the lung for carbon monoxide (DLCO) and VEGF correlated with inspiratory capacity/total lung capacity, DLCO, and BODE. There were no significant sex differences in plasma biomarkers in the control group. Sex differences in bronchoalveolar lavage protein expression in COPD patients have been reported by Kohler *et al.* [28], who found a subset of 19 proteins that distinguish healthy female smokers from COPD patients with 78% discriminative power. These authors speculate that downregulation of the lysosomal pathway and upregulation of the oxidative phosphorylation pathway linked dysregulation of macroautophagy to a female-predominant COPD disease phenotype. Consideration of sex-specific differences is essential in all types of future research [29,30].

CHRONIC OBSTRUCTIVE PULMONARY DISEASE AND RACE

Far less information is available concerning risk for COPD or early-onset COPD in African-Americans. Most recent data involve the genetics of nicotine metabolism. The genetic locus on chromosome 15q24–q25.1 containing the *CHRNA5–CHRNA3–CHRNA4* cholinergic nicotinic receptor subunit gene cluster has been associated with nicotine dependence, lung cancer, and cigarettes smoked per day [31,32]. Saccone *et al.* [33] genotyped a panel of single nucleotide polymorphisms (SNPs) in a cohort of African-Americans and individuals of European ancestry. The nonsynonymous *CHRNA5* SNP, rs16969968, was the most significant SNP associated with nicotine dependence in the full sample ($n = 2772$), odds ratio (OR) 1.42 (1.25–1.61), $P = 4.49 \times 10^{-8}$ with stronger, concordant association in African-Americans, OR 2.04 (1.15–3.62), $P = 0.015$. A genome-wide association study meta-analysis of 32 389, African-Americans in the Study of Tobacco in Minority Populations Genetics Consortium, was published in 2012 [34]. Although a few other SNPs approached genome-wide significance, only rs2036527, a noncoding SNP in the 5'-distal enhancer region on chromosome 15q25.1 reached genome-wide significance for association with cigarettes smoked per day, $P = 1.84 \times 10^{-8}$. A subsequent meta-analysis was performed on a cohort of 32 587 smokers from three ethnic groups; European ($n = 14\,786$), African-American ($n = 10\,912$), and Asian ($n = 6889$). This analytic strategy was used because a comparison of associations across diverse populations could assist in narrowing and defining the region of interest and yield variants more likely to have functional consequences. The authors found association between smoking quantity and variants on chromosome 15q25 in all groups. Again, rs16969968 was associated with smoking in all groups, $P < 0.01$. In the meta analysis across all populations, the OR was 1.33 (1.25–1.42), $P = 1.1 \times 10^{-17}$. As the findings for this variant were concordant across groups when other associations were not, the authors suggested that rs16969968 was the most likely functional variant for association with heavy smoking.

Han *et al.* [35] hypothesized that health-related quality of life (QOL) in COPD patients differs by race and sought to determine the characteristics that influence QOL. African-Americans were less well educated, younger, and more likely to actively smoke. In patients who did not experience exacerbations in the past year, QOL was similar to that reported by white COPD patients. However, African-Americans were twice as likely to report an

exacerbation that required hospitalization and those patients reported worse QOL. In a study of the overlap between asthma and COPD, Hardin *et al.* [36] found that African-Americans were twice as likely to report a history of asthma (33.6 versus 15.6%, $P < 0.001$). Patients with COPD and asthma experienced worse QOL, were nearly four times more likely to experience frequent exacerbations, OR 3.55 (2.19–5.75), $P < 0.0001$, and had more radiographic gas trapping on computed tomography.

CONCLUSION

Sufficient evidence exists to support substantial sex-specific differences in COPD susceptibility, symptoms, and comorbidities. Better understanding of these differences may result in new therapeutic strategies and targets. In contrast, there is insufficient mechanistic research into racial disparities in COPD allowing detangling from social and environmental effects. As COPD patients of the future will progressively include women and minorities, justification for such research, targeted preventive strategies, and new therapeutics are needed.

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- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 183–184).

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KEY POINTS

- Biomarkers for COPD and their relationship to clinical and physiologic factors vary by sex in COPD patients.
- Downregulation of the lysosomal pathway, upregulation of the oxidative phosphorylation pathway, and dysregulation of macroautophagy have been proposed by a single center study as an explanation for a female-predominant COPD disease phenotype.
- African-Americans with COPD are significantly younger, smoke less, report concurrent asthma more frequently, and have less radiographic emphysema on volumetric computed tomography.