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CHRONIC OBSTRUCTIVE PULMONARY DISEASE: OCCURRENCE AND ASSOCIATIONS WITH OCCUPATIONAL EXPOSURES AND SMOKING

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide. Presently COPD is the fourth leading cause of death, responsible for more than 3 million deaths in 2012 and accounting for 6% of all deaths globally. It is projected that by 2020 COPD will be the third leading cause of death.[1] With regard to Ontario, Statistics Canada estimated in 2014 that 4.3% of Ontarians live with COPD, with estimates ranging as high as 12%.[2]

Diseases of the airways include bronchitis affecting the large airways, small airways disease (SAD), asthma, and COPD. Bronchitis manifests clinically as cough and sputum production. SAD manifests clinically as decreased air flow in the small airways of the lung, with reduced FEF_{25-75} and FEF_{75}. Asthma is airway hyper reactivity with reversible airway obstruction; symptoms are cough, wheeze, chest tightness, and shortness of breath. The basic mechanism for each of these diseases is inflammation. COPD is chronic irreversible airway obstruction with respiratory symptoms similar to those of asthma, with the exception of chest tightness which tends to be less prominent with COPD. Chronic bronchitis, chronic asthma, and SAD are associated pathophysiologically with development of COPD, as is emphysema, a disease of the alveoli or air sacs in the lung.

Smoking is the most common cause of COPD, but non-smokers are also diagnosed with COPD. The U.S Department of Health and Human Services/Centers for Disease Control and Prevention (CDC) recently estimated that 24% of adults with COPD have never smoked.[3] Population-attributable fractions (PAF) for smoking range from 9.7 to 97.9%, with the majority of PAF estimates being less than 80%.[4] Variability in prevalence is related to gender and age of the study population, the proportion of smokers, diagnostic criteria used, and differences in methods used to calculate PAF; it is higher in industrialized countries than in developing countries. Published data indicate that factors other than smoking, or in addition to smoking, are important contributors to the development of COPD. These factors include genes; chronic asthma; air pollution; second-hand smoke; occupational exposures to vapors, gases, dusts, and fumes (VGDF); exposure to wood smoke and biomass fuels used in heating and cooking; and frequent pulmonary infections in childhood.[2,4] COPD is associated with a number of co-morbidities and is believed to contribute independently (of smoking) and causally to increase in risk for lung cancer.

The purpose of this paper is to review COPD and etiologic factors that have been shown to be important to development of disease. COPD is a preventable disease. Understanding etiologic factors is necessary for reducing risk for disease and improving prognosis once COPD has been diagnosed. The impact of Interactions between occupational exposures and smoking on risk for disease will be examined. A companion piece will explore dose-response relationships between dust exposures and risk for COPD.

DEFINITION

The Science Committee of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in its 2018 Report defined COPD as “a common, preventable and treatable disease that is

characterized by persistent airway symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases."[1] The American Thoracic Society (ATS) in its examination of published epidemiologic evidence in order to assess the global burden of COPD and novel risk factors used three broad definitions of COPD: spirometry-based (e.g., GOLD FEV1/FVC < 0.70); symptom-based, specifically chronic bronchitis (cough and sputum production for $\geq$ 3 months/year for $\geq$ 2 consecutive years); and self-reported physician diagnosis of chronic bronchitis, emphysema, or COPD.[4] The weight given to each study depended on the definition of COPD, with greatest weight being given to those studies that used spirometry-based definitions and the least to those studies reliant upon self-report.

Chronic bronchitis and emphysema have been used clinically in the past to indicate obstructive airways disease. Diagnosis of the former is symptom-based and of the latter, pathology-based. Timens *et al.* in *Spencer's Pathology of the Lung* describe three pathologic components of COPD.[5] These are chronic bronchitis and bronchiolitis, affecting the large and small airways, respectively, and emphysema. Anatomy and clinical characteristics of these conditions vary. The basic mechanism, inflammation, does not. The importance of external exposures to the development of COPD is clear from the anatomical relationship between the respiratory tract and the external environment. The airways are in open communication with the environment and lead directly to the alveoli. Inhaled particulate and gaseous matter cause inflammatory changes in the airways, the alveoli, or both depending on particle size and solubility.

The ATS in its Public Policy Statement of 2010 recognizes the heterogeneity of COPD, noting chronic airflow obstruction as the single common denominator.[4] The criterion used by GOLD, the ATS, and the British Thoracic Society to define airflow obstruction is post-bronchodilator FEV1/FVC < 0.70.[1,4,6] The basic pathophysiologic mechanism is inflammation. Disease of the small airways occurs early-on and predicts progression of COPD and functional decline in FEV1.[7-9] SAD manifests physiologically as decreased airflow at 25-50% and 75% of vital capacity (FEF_{25-50} and FEF_{75}) on spirometry.[1] Because these findings are nonspecific and will likely precede the development of obstruction defined as FEV1/FVC < 0.70, they are often overlooked or ignored. The significance of SAD has been considered somewhat controversial in the past.[9] As we are becoming better able to detect, measure, and monitor SAD using physiologic, tomographic, and other tools, it may emerge as an important component of the definition of obstruction and therefore of COPD.[8,9] At the very least, in the context of exposure to cigarette smoke and/or occupational exposure to VGDF, evidence of SAD may provide an opportunity for prevention of COPD as currently defined.

DIAGNOSIS

Diagnosis of COPD depends upon suspecting the diagnosis. Guidelines recommended by the British Thoracic Society state that breathlessness, chronic cough, sputum production, "frequent winter bronchitis", and wheeze suggest COPD in at-risk individuals over the age of 35 years.[6] GOLD advises that COPD should be considered in those with typical respiratory symptoms and/or risk factors for disease. Warning signs are persistent dyspnea, progressive over time and worse with exertion; chronic cough; chronic sputum production; and recurrent wheeze.[1] A history of

frequent respiratory tract infections may be an indicator. Risk factors include host factors such as positive family history, tobacco smoke, smoke from home cooking and heating fuels such as biomass, and occupational exposure to VGDF. The greater the number of variables present, the greater the likelihood of disease. Risk factors on their own may be sufficient to warrant further investigation.

A diagnosis of COPD must be confirmed with objective measurements.[1,6] Because physical evidence of disease is generally not present until disease is in advanced stages, physical examination may provide support for a suspected diagnosis but it is not confirmatory. There is consensus that spirometry is "the most reproducible and objective measurement of airflow limitation."[1]

Confirmation of the diagnosis of COPD is based upon post-bronchodilator FEV1/FVC < 0.70.[1,4,6] Asthma can mimic COPD, and vice versa, so that the magnitude of the bronchodilator response should be taken into account in diagnostic considerations and treatment decisions. It is important to note that improvement in the FEV1/FVC ratio to > 0.70 does not equate with resolution of disease.[10] Such a transition may be attributable to decline in FVC, as Guillamet *et al.* point out, or to successful treatment with medication and/or removal from toxic exposures.

The recommendation of the use of the absolute ratio as the criterion for diagnosis is based upon its simplicity, its freedom from reference values, and its common use in epidemiologic studies that provide basis for existing guidelines.[1] There are also epidemiologic data to support the use of lower and upper limits of normal (LLN, ULN, respectively) to define the normal range. Clinically obstruction is often defined as FEV1/FVC < LLN for FEV1/FVC. The LLN for spirometric parameters is based upon the 95% confidence interval around a mean value determined on the basis of epidemiologic studies of representative populations. Age, gender, race, and ethnicity are variables that are examined in developing prediction equations.[11] In addition, socioeconomic factors have been taken into account. For example, predicted values more relevant to blue collar workers have been derived from studies of blue collar workers.[12]

To be reliable, pulmonary function test results must be reproducible and acceptable using criteria set forth by the ATS and the European Respiratory Society.[1,13,14] A comment on patient effort by the pulmonary technician performing the lung function tests is helpful to assessment of reliability of test results. However, test results that are not reproducible should not be attributed automatically to poor effort as epidemiologic studies have shown that participants with respiratory disease are less likely to perform spirometry reproducibly.[15] The exclusion of these participants on the basis that they are not giving full effort is likely to bias results toward the null (i.e., there is no association with exposures such as VGDF or cigarette smoke).

Spirometry is used not only to diagnose COPD and but also to determine severity.[1] The algorithm recommended by GOLD is as follows: GOLD 1: mild, FEV1 $\geq$ 80% predicted; GOLD 2: moderate, 50% $\leq$ FEV1 < 80% predicted; severe GOLD 3: 30% $\leq$ FEV1 < 50% predicted; GOLD 4: very severe FEV1 < 30% predicted. Lung volumes and single breath diffusing capacity for carbon monoxide (DLCO) are important to further characterizing the nature and severity of disease in an objective

manner. For example, increase in lung volumes outside the normal range (> 120% predicted or > ULN) indicate air trapping that may be the consequence of SAD and/or emphysema. A normal total lung capacity in the presence of reduced FEV1/FVC, or with other indicators of obstruction but normal FEV1/FVC, may indicate co-existent restriction. Reduction in DLCO in the presence of obstruction indicates impaired gas exchange likely due to emphysema, in the absence of other causes of impairment in gas exchange.

COPD is a complex chronic condition. In some cases, its diagnosis is straightforward and clear-cut. In other cases it is complicated by other or co-existent disease such as asthma or a restrictive ventilatory deficit caused by interstitial fibrosis. It is associated with a number of co-morbidities that may obscure the clinical picture and make COPD diagnosis more difficult. These include heart disease, pulmonary hypertension, musculoskeletal dysfunction, and metabolic syndrome. COPD is a risk factor for lung cancer independent of co-existent exposures to lung carcinogens such as cigarette smoke.[16] Early diagnosis and determination of causal attribution is key because it provides the opportunity to prevent worsening of respiratory symptoms and lung function.

ETIOLOGY: OCCUPATIONAL EXPOSURES

General

As Naidoo reminds us in his editorial entitled "Occupational exposures and chronic obstructive pulmonary disease: incontrovertible evidence for causality?", it was in 1984 that the U.S. Surgeon General published a report arguing that up to 90% of cases of COPD were caused by smoking. And only one year later that Margaret Becklake published an article describing the relationship between chronic airflow limitation and work in the dusty trades.[17-19] In 1989 Becklake authored a review setting forth evidence for a causal association between occupational exposures and the development of COPD.[20] She reviewed the published scientific literature on respiratory health effects of occupational exposure to airborne dusts, vapors, and fumes, with a focus on chronic obstructive airway disease. Becklake concludes "This evidence, reviewed here according to accepted criteria for establishing causality, leaves little doubt that occupational exposure to dust and/or to dust and fumes may be causally implicated in the genesis of COPD." Over time evidence supporting such an association has grown substantially.

GOLD in its 2001 report identified both host and environmental risk factors for the development of COPD.[21] Environmental risk factors included tobacco smoke and occupational dusts and chemicals. With regard to the latter, the Scientific Committee wrote "When the exposures are sufficiently intense or prolonged, occupational dusts and chemicals (vapors, irritants, fumes) can cause COPD independently of cigarette smoking and increase the risk of the disease in the presence of concurrent cigarette smoking." In 2003 the ATS published an Official Statement on "Occupational contribution to the burden of airway disease."[22] In preparing this document, a committee of the ATS conducted an extensive review of existing published literature, including case reports and cross-sectional, case-control, and cohort studies, in order to quantify the contribution of workplace exposures to the burden of asthma and COPD. Among the difficulties encountered for COPD was the historic lack of a standardized definition. The committee

concluded that a reasonable estimate of population-attributable risk (PAR) for occupational exposures in the case of COPD was 15%.

The importance of SAD in the development of COPD is discussed above.[7-9] In their review of the epidemiology and pathology of COPD caused by occupational exposure to silica dust, Hnizdo *et al.* discuss SAD attributable to mineral dust exposure (MDAD) more generally.[23] SAD is detectable physiologically and pathologically. Physiologically SAD manifests as decreased airflow in the small airways of the lung (FEF_{25-75}, FEF_{75}). Pathologically the disease affects the respiratory bronchioles and alveolar ducts, with the respiratory bronchioles being affected first. In the case of MDAD, described early on by Churg *et al.*, peribronchiolar fibrosis and pigment changes are common.[24] Compared to SAD in smokers, MDAD is characterized by marked thickening and fibrosis of the wall of the respiratory bronchiole and the presence of golden iron and/or black carbon pigment *vs.* thinner bronchiolar walls and a relative paucity of pigment seen in smokers.

Of 53 dust-exposed workers evaluated by Churg *et al.*, 25% (n=13) had evidence of MDAD compared to 0.8% (1 of 121) non-mineral-dust exposed subjects.[24] Pathologic changes affected not only the respiratory bronchioles but also the membranous bronchioles. Compared to 53 unexposed subjects, significant declines in FEV_{25-75}, FEV1, FVC, and DLCO were observed in the exposed group with MDAD, as was increase in RV/TLC consistent with obstruction and air trapping. Age and smoking habits of the two groups were similar. These findings are particularly significant given the likely etiologic importance of SAD and MDAD to COPD.

The ATS in its 2010 Public Policy Statement concludes that existing evidence supports a causal association between occupational exposures to VGDF and the development of COPD.[4] The stated bases for its conclusion are several. The data were obtained from "high quality" epidemiologic studies, using variable definitions of COPD: respiratory symptoms, spirometric evidence of obstruction, physician diagnosis, and mortality. The evidence includes demonstrated dose-response relationships and temporal associations. Experimental studies in animals have shown development of pathologic changes consistent with chronic bronchitis and/or emphysema following exposure to agents shown to be associated with COPD in epidemiologic studies of humans.

A case-control study of COPD and occupational exposures was carried out by Weinmann *et al.* in adult members of Kaiser Permanente Northwest (KPNW), a large managed care organization.[25] Cases were selected on the basis of lung function test results that met criteria for obstruction defined as FEV1/FVC < LLN using prediction equations from the NHANES III survey.[11] A telephone interview survey was then conducted of cases (n=388) and controls (n=356). Experienced certified industrial hygienists from KPNW and the National Institute of Occupational Safety and Health (NIOSH) assessed and categorized workplace exposure histories.

Weinmann *et al.* observed Increased OR's among all subjects for *mineral dust* (odds ratio (OR) 1.7, 95% confidence interval (CI) 1.1-2.7), *irritant gases and vapors* (OR 1.6, 95% CI 1.2-2.2), *diesel exhaust* (OR 1.9, 95% CI 1.3-3.0), *irritant gases or vapors* (OR 1.6, 95% CI 1.2-2.2), and the composite sensitizers, organic solvents (GVSS) (OR 1.7, 95% CI 1.2-2.4).[25] The number of never

smokers was small (n=100); but in this group significant or borderline-significant increases in OR were observed for mineral dust (OR 3.5, 95% CI 0.94-13.3), diesel exhaust (OR 6.4, 95% CI 1.3-31.6), GVSS (OR 2.3, 95% CI 0.96-5.6), and any dust, GVSS or diesel exhaust (OR 2.4, 95% CI 0.99-5.6). When examined by level of exposure (low vs. high), among smokers OR for the following exposures at high levels were statistically significant: metal dust, mineral dust, gases/vapors, dust composite, and dust/GVSS/diesel composite. For diesel exhaust and GVSS composite OR for low-level exposure were significant. Consistent with the recognition of chronic asthma as a novel risk factor for COPD, personal history of asthma was significantly associated with COPD in both ever and never smokers in the current study ($p < 0.05$).[4,25]

Omland *et al.* conducted a systematic search of the published scientific literature for peer-reviewed epidemiologic studies of associations between occupational exposures and COPD.[26] Of 4,528 citations found, the authors selected 147 for review. Criteria for selection included pulmonary function testing, sufficient occupational history, and use of external or internal referents. Ten panel members who conducted the review included occupational physicians, pulmonary physicians, and experts in respiratory physiology from five different countries. Occupational exposures to the general category VGDF and more specifically to inorganic and mineral dusts and to organic and biologic dusts were examined. Of the studies reviewed, only two were studies of coal and gold miners. These were not included in the general analysis because of potentially confounding factors such as co-existent pneumoconiosis and/or tuberculosis. Despite the heterogeneity of study populations and study designs, the authors found consistency of association between occupational exposures and COPD. Exposure preceded the development of disease, satisfying Sir Austin Bradford Hill's criterion of temporal association for *causation*.[27] Dose-response relationships were observed in more recently-conducted studies. Despite limitations introduced by variability in determination of definition of "COPD" and the use of a fixed ratio to define obstruction, the authors concluded that there was "strong evidence" of a causal association between occupational exposures and development of COPD.

The Collegium Ramazzini, an international organization of 180 occupational and environmental health professionals, issued a position statement in 2016 entitled "A New Approach to the Control of Chronic Obstructive Pulmonary Disease (COPD)."[28] The Collegium committee reviewed published epidemiologic and experimental studies of relationships between exposure to vapors, gases, dusts, and fumes and development of COPD, as well as existing regulatory standards for workplace exposures. The Collegium advised the use of a new paradigm to improve recognition and regulation of risks associated with occupational exposures to VGDF, namely to recognize and regulate *mixtures* of agents rather than a single agent at a time, as such mixed exposures are the reality for most workers. Similarly, the Collegium advised recognition and consideration of combined risks from tobacco smoke, occupational exposures, and environmental exposures as etiologically important in development of COPD and in its prevention.

Specific

Epidemiologic studies of work and COPD have revealed significant associations with specific occupations and occupational exposures. Using data from the Third National Health and Nutrition Examination Survey (NHANES III) collected during the period 1988 to 1994, Hnizdo *et al.* estimated that 19% of cases of COPD in the United States are attributable to workplace exposures.[29] NHANES surveys are conducted on a continuous basis and released in two-year cycles. The surveys consist of a detailed in-home telephone interview and a subsequent physical examination that includes spirometry. In the Hnizdo study COPD was defined by spirometry as FEV1/FVC < 0.70 and FEV1 < 80% predicted, the GOLD criteria in use at that time. Among nonsmokers, the PAR was 31%. Among all subjects with COPD, there was a 20% increase in risk for the occupational category of laborer or other construction trades worker (OR 1.2, 95% CI 0.6-2.5); for nonsmokers, observed OR was 3.4 (95% CI 1.1-10.5). For the occupational grouping that included laborers or other construction workers, there was increasing risk with increasing duration of work at the trade: for 1-14 years, OR 1.4 (95% CI 1.0-1.9); for $\geq$ 15 years, OR 1.5 (95% CI 1.2-2.0).

In 2019 Kurth *et al.* reported the results of their examination of airflow obstruction and work in the U.S. using data from three NHANES surveys: 2007-2008, 2009-2010, and 2011-2012.[30] Data were obtained and analyzed for ever-employed U.S. adults ages 18 to 79 years by industry and occupation. Airflow obstruction was defined on the basis of spirometry: pre-bronchodilator values showing FEV1/FVC < LLN; when FEV1 was < 70% of predicted, additional analysis was undertaken to determine severity of obstruction. Employment history was based on the longest-held job.

The number of participants was 13,044. Prevalence of airflow obstruction was 7.15% among never smokers and 18.47%% among ever smokers. By industry, the highest prevalence was observed for mining where prevalence of airflow obstruction was 22.66% (95% CI 10.78-34.54) and a twofold increase in prevalence odds ratio (POR) was observed (POR 2.04, 95% CI 1.05-3.97). Significant Increases in POR were also observed for workers employed in the manufacture of motor vehicles and motor vehicle equipment (POR 1.66, 95% CI 1.20-2.30), construction (POR 1.64, 95% CI 1.26-2.13), and services to buildings, landscaping, and waste management (POR 1.57, 95% CI 1.08-2.27). POR was adjusted for age, gender, race/Hispanic origin, and smoking status. By occupation, the highest prevalence was observed for extraction at 34.49%; increase in POR was significant at 3.82, 95% CI 1.55-9.43. Significant increases in POR were also observed for bookbinders and printers (POR 3.14, 95% CI 1.56-6.30); installation, maintenance, and repair (POR 3.11, 95% CI 1.48-6.55); and construction laborers and construction trades helpers (POR 1.94, 95% CI 1.28-2.94). Potential occupational exposures cited for miners and extraction workers were diesel exhaust; volatile organic compounds; polycyclic aromatic hydrocarbons; fumes; dusts such as silica, coal dust, and metallic compounds; as well as “other chemicals.”

Using the same NHANES dataset, Doney *et al.* examined associations between self-reported occupational exposures and airflow obstruction and self-reported COPD.[31] Airflow obstruction was determined on the basis of spirometry showing FEV1/FVC < LLN. Self-reported COPD was

defined as a positive response to the questions have you ever been told by a physician or other health care professional that you have chronic bronchitis and that you still have chronic bronchitis, or that you have emphysema. Occupational exposures queried were for any of their jobs, as was number of years of exposure. In addition to specific self-reported workplace exposures, a COPD-job exposure matrix (JEM) previously constructed by the National Institute of Occupational Safety and Health (NIOSH) was used to assign level of exposure (low, medium, high).

POR for self-reported occupational exposure to organic dust was significantly elevated for airflow obstruction and for self-reported COPD: POR 1.23, 95% CI 1.05-1.44; and 1.64, 95% CI 1.29-2.08, respectively. For self-reported COPD, POR's were significantly elevated for the following: mineral dust (POR 1.62, 95% CI 1.19-2.21); exhaust fumes (POR 2.01, 95% CI 1.48-2.74); other gases/vapors/fumes (POR 1.47, 95% CI 1.20-1.79); and ever dust and/or fumes (POR 2.04, 95% CI 1.64-2.53). Elevation in POR for exhaust fumes and airflow obstruction was borderline significant (POR 1.13, 95% Ci 0.97-1.31). Prevalence of airflow obstruction and of self-reported COPD was significantly elevated among ever smokers and never smokers, for overall occupational exposures and for specific exposures (mineral dust, organic dust, exhaust fumes, other gases/vapors/fumes, and ever dust and/or fumes). Prevalence was higher among ever smokers. The authors concluded that airflow obstruction and self-reported COPD are associated with workplace exposures determined by self-report and JEM-assignment in a nationally-representative study.

Mabila *et al.* used data from the U.S. National Health Interview Survey (NHIS) conducted 2006-2015 to examine risk for obstructive airways disease in mining occupations, stratified by dust exposure level.[32] The NHIS is a cross-sectional telephone-interview survey of non-institutionalized adults in the United States conducted on an annual basis by the National Center for Health Statistics. With regard to industry, participants with the industry code of "mining" were classified as miners; the type of mine was not specified. Those with industry codes for oil and gas extraction were excluded. Chronic bronchitis, emphysema, and asthma were each defined as positive responses to the questions "During the past 12 months have you been told by a doctor or other health professional that you have" chronic bronchitis, emphysema, or asthma, respectively. COPD was determined on the basis of positive response to the question for either chronic bronchitis or emphysema. Mine dust exposures were categorized as low, moderate, high, and very high. Extraction workers defined as drillers, blast/explosive technicians, long wall operators, roof bolters were considered to be very highly exposed.

The number of mining workers who participated in the NHIS surveys during the period in question was 1,531. Of these, 44.3% gave mining as their occupation of longest duration; 44.7% were never smokers. In multivariate analysis controlling for age, gender, race, and smoking status, significant increase in OR using the low exposure group as a referent was observed for chronic bronchitis, emphysema, and COPD in the very high exposure group: OR 2.18 (95% CI 1.02-4.64), 7.85 (95% CI 1.70-36.27), and 2.56 (95% CI 1.29-5.12), respectively. The finding of significant increase in OR for these disease outcomes while taking into account smoking status (never,

former, current) provided support for the independent association between exposure to respirable mineral dust and development of COPD, in the stated view of the authors.

Using data from the NHIS survey 2013-2017, Syamlal *et al.* examined the prevalence of COPD in a representative sample of never-smoking adults age 18 or older by industry and occupation.[3] Definition of COPD was a positive response to one or more of the following questions: 1) "Have you ever been told by a doctor or other health professional that you had chronic obstructive pulmonary disease, also called COPD?" 2) "Have you ever been told by a doctor or other health professional that you had emphysema?" 3) During the past 12 months, have you been told by a doctor or other health professional that you had chronic bronchitis?" Respondents were considered never smokers if they had never smoked or if they had smoked less than 100 cigarettes in their lifetime.

In a representative sample of the estimated population of 164 million adults in the United States working at any time during the 12 months preceding the interview, COPD prevalence was 6.0% (3.4 million) among ever-smokers and 2.2% (2.4 million) among never-smokers.[3] Prevalence varied by age, gender, self-perceived health, and industry and occupation. For each of these variables, prevalence was uniformly higher among women than men. Among adults overall age $\geq$ 65 years, prevalence was 4.6 (95% CI 3.8-5.4). For those who self-reported poor/fair health, prevalence was 7.8 (95% CI 6.4-9.2) among women and 5.3 (95% CI 3.9-6.7) among men. With regard to industry, significant elevation in COPD prevalence were observed for women but not men for wholesale trade, transportation and warehousing, and information at 4.6 (95% CI 2.5-6.7), 4.3 (95% CI 2.6-5.9), and 5.1 (95% CI 2.8-7.3), respectively. With regard to occupational groups, the highest COPD prevalence was observed among women for the following: office and administrative support (4.0, 95% CI 3.3-4.6), production (4.4, 95% CI 2.0-6.8), and transportation and material moving (4.5, 95% CI 2.1-6.8).

In this survey, 35% of respondents were ever smokers and 65%, never smokers. Among ever-smokers, 3.8% reported chronic bronchitis, while 1.1% and 2.5% reported emphysema and COPD, respectively. For never-smokers 1.9% reported chronic bronchitis and 0.1% and 0.4% emphysema and COPD, respectively. Thus, chronic bronchitis was reported 3.5 times more frequently than emphysema by ever smokers, and 19 times more frequently by never smokers, suggesting that COPD is more often caused by chronic bronchitis among never smokers compared to ever smokers.

Railroad workers with the potential for exposure to diesel exhaust, silica, and asbestos dust have been shown to be at increased risk for COPD mortality. In a case-control study of railroad workers exposed to diesel exhaust, Hart *et al.* observed a significant increase in risk for COPD mortality among railroad engineers and conductors, taking smoking into account.[33] For those with $\geq$ 16 years of work for the railroad, OR 1.67 (95% CI 1.17-2.39) was observed. Test for trend (increasing risk for COPD mortality with increasing years of work for the railroad) was significant ($p = 0.01$). A similar increase in risk for COPD mortality was observed by Hart el al in a cohort study of railroad workers followed from 1959 to 1996.[34] For engineers and brakemen hired after 1945

with ≥ 20 years of work for the railroad, HR 1.67 3.3 (95% CI (95% CI 1.03-2.71) was observed, controlling for smoking.

On March 25, 2016, the U.S. Occupational Safety and Health Administration (OSHA) promulgated its silica standard: *Occupational Exposure to Respirable Crystalline Silica; Final Rule*.[35] The current silica standard reduces the permissible exposure limit (PEL) for respirable crystalline silica from 100 µgm/m3 to 50 µgm/m3. Among the bases cited by OSHA for its regulatory decision to decrease the PEL was the increase in risk for non-malignant respiratory disease (NMRD) shown to be associated with occupational exposure to respirable crystalline silica. OSHA concluded that there is a dose-response relationship between respirable crystalline silica and risk for NMRD, exclusive of silicosis. These NMRDs are primarily COPD, chronic bronchitis, and emphysema. OSHA further concluded that "the risk is strongly influenced by smoking and opined that the effects of smoking and silica exposure may be synergistic" (p.16310).

ETIOLOGY: OCCUPATIONAL EXPOSURES AND SMOKING

Independent effects of VGDF on risk for COPD in smokers have been acknowledged by GOLD and observed and reported by Mabila.[21,32] Others have shown not only independent and additive effects of smoking and occupational exposure to VGDF on risk for COPD, but also an interactive effect such that the joint effect is greater than additive - in a manner similar to that of smoking and asbestos on risk for lung cancer.

Hnizdo *et al.* examined the impact of combined silica dust exposure and smoking on airflow obstruction in published studies of Canadian and U.S. hard rock miners exposed to silica.[23] Different patterns of pulmonary function were observed in non-smokers compared to smokers. In non-smokers, observed ventilatory deficits were suggestive of restriction, with reduction in residual lung capacity. Smokers, on the other hand, had findings more consistent with obstruction, with reduction in FEV1, FVC, FEV1/FVC, and maximal expiratory airflow rates, and increase in residual lung capacity. Physiologic abnormalities increased with increasing silica dust exposure levels.

In an earlier study of 2,209 South African gold miners, Hnizdo *et al.* examined effects of increasing silica dust exposure and smoking on lung function.[36] Spirometry was performed and an abnormal test result defined as a value < LLN. Air flow rates, FEV1/FVC, and FVC were measured. The following ventilatory deficits were defined: minimal obstruction, moderate obstruction, marked obstruction, marked combined obstruction/restriction, and restriction. Respiratory impairment was examined by smoking status (nonsmoker, ex-smoker, current smoker) and by dust exposure at levels up to 52,000 particle-years. The effect of increasing dust exposure up to 40,000 particle-years on decline in lung function was greatest for the small airways (FEF_{25-75}) in current smokers. With regard to ventilatory deficits, a trend for increasing prevalence with increasing dust exposure was observed for ex- and current smokers with moderate obstruction and for current smokers with marked obstruction and marked obstruction/restriction. A similar trend was not observed for nonsmokers. Among those with marked obstruction or marked combined obstruction/restriction, risk was highest for heavy smokers at higher dust exposures (OR 10.4

(95% CI 5.6-19.4)). The PAF for silica dust alone was 8%; for smoking alone, 42%; and for the combination of the two, 40%. These findings indicate a higher prevalence of more severe obstruction among occupationally-exposed miners who smoke than among miners who do not smoke, and support an interactive effect of occupational exposure to silica dust and smoking on risk for COPD.

Trupin *et al.* conducted a telephone interview survey of 2,061 randomly-selected U.S. residents' ages 55-75 years.[37] Respiratory health (chronic bronchitis, emphysema, COPD, and asthma), general health, and occupational exposures were queried. Those reporting chronic bronchitis alone were subsequently excluded from data analysis. Information about occupational exposures was obtained using a question from the European Community Respiratory Health Survey (ECHRHS). Based upon self-reported occupational exposures, a job-exposure matrix (JEM) created for the ECHRHS was applied. Both self-reported exposures and the JEM were applied in data analysis.

Associations between COPD or emphysema and occupational exposures to VGDF and cigarette smoke were examined. Adjusted OR for exposure to VGDF alone was 2.4 (95% CI 0.9-6.1); for smoking alone, 7.0 (95% CI 3.6-13.7). For the two together, adjusted OR was 18.4 (95% CI 9.3-36.4), indicating that the effect of both together was greater than either alone, with the numbers suggesting a multiplicative effect. The authors concluded "In the present analysis, evidence was found for an interaction between smoking and occupational exposures, such that current or former smokers reporting job exposure were at particularly high risk of COPD."

Blanc *et al.* conducted a nested case-control analysis of data obtained as part of a prospective cohort study of COPD in adult members of a managed health care organization.[38] One of the purposes of the analysis was to examine separate and combined effects of smoking and occupational exposure to VGDF on risk for COPD. Cases were chosen on the basis of meeting both a healthcare-utilization criterion and a medication-prescribing criterion. Required to meet the healthcare-utilization criterion was one or more ambulatory visits or emergency department visits or hospitalizations with a principal ICD-9 diagnostic code for chronic bronchitis, emphysema, or COPD during the preceding 12 months. Required to meet the medication-prescribing criterion was two or more prescriptions for COPD-related medication during the preceding 12 months. Occupational exposure information and smoking history were obtained from structured telephone interviews and, for occupational exposures, a JEM. Blanc *et al.* observed a twofold increase in risk of COPD among cases (OR 2.11, 95% CI 1.59-2.82) for self-reported occupational exposure to VGDF during the longest-held job, adjusting for smoking, age, gender, and race. Estimated PAR was 31%.

Analysis of joint associations between smoking and occupational exposure to VGDF on COPD risk for the group as a whole revealed adjusted OR 1.98 (95% CI 1.26-3.09) for occupational exposures alone and OR 6.71 (95% CI 4.58-9.82) for cigarette smoking alone. For the two together, an OR of 14.1 (95% CI 9.33-21.2) was observed, a finding consistent with that of Trupin *et al.* (2003) and suggestive of a multiplicative effect. For those with GOLD II COPD (FEV1/FVC < 0.70, 50% $\leq$ FEV1 < 80% predicted) results were similar, with OR 1.69 (95% CI 0.96-2.97) for occupational exposure

alone; OR 8.31 (95% CI 5.27-13.1) for smoking alone; and OR 18.7 (95% CI 11.6-30.0) for both together.

Boggia *et al.* examined associations between COPD and occupational exposure to "welder smokes, gases, or chemical irritants for the airway" and cigarette smoking in a group of 2,019 workers in different sectors in Southern Italy.[39] Exposure information was obtained from the workers themselves. Smoking was defined as follows: non-smoker – never smoker or "quit smoking for more than 10 years at the baseline"; smokers – smoked > 5 cigarettes/d for > 5 years. COPD was defined on the basis of respiratory symptoms consistent with the standardized definition of chronic bronchitis (cough and phlegm on most days for three months or more per year for at least two consecutive years) and spirometry (FEV1/FVC < 0.70 and FEV1 < 80% predicted). Based on workplace exposures and smoking, participants were divided into four groups: group 1: non-smoker without professional occupational exposures as defined (n=261, 12.9%); group 2: smoker without professional occupational exposures (n=676, 33.5%); group 3: non-smoker with professional occupational exposures (n=242, 12%); and group 4: smokers with professional occupational exposures (n=838, 41.5%).

Prevalence of COPD varied by group at baseline in 1995, at first follow-up in 2000, and at second follow-up in 2005, with groups 3 and 4 having the highest prevalence at each of the three examinations. For group 1, the referent group, COPD prevalence was 3.1% at baseline; 4.0% at second exam; and 5.2% at the third exam. Prevalence for group 2 was 6.7%, 7.9%, and 11%, respectively; for group 3, 9.1%, 11.5%, and 16.3%, respectively. For group 4, the group with combined occupational and cigarette smoke exposures, prevalence of COPD was 13.8%, 18.3%, and 23.4%, respectively. Chi-square for difference in prevalence among the four groups was statistically significant at baseline and at each follow-up. Significance levels at 10 years are as follows: for smoking alone $p < 0.01$, occupational exposures alone $p < 0.001$, and for combined exposures vs. not exposed $p < 0.001$. Significant ORs (Exp (β)) were observed for cigarette smoking, for occupational exposures, and for the interactive effect of cigarette smoking-occupational exposures at 1.75 (95% CI 1.27-2.41), 2.62 (95% CI 2.02-3.41), and 2.51 (95% CI 1.97-3.20), respectively. These findings support the independent and positive effect of occupational exposure to vapors, gases, dusts, and fumes on risk for COPD. Both prevalence data and logistic regression analysis indicate a risk for COPD from workplace exposures alone that is greater than the risk from smoking alone.

Kurth *et al.* studied the prevalence of airflow obstruction by longest-held job using spirometry to define obstruction.[40] Data were obtained from combined cross-sectional results of the NHANES 2007-2008 and 2009-2010 household interview surveys. Airflow obstruction was defined using the ATS/European Respiratory Society criterion of FEV1/FVC < LLN. For participants 18 and 19 years of age, never smoking was defined as using neither tobacco nor nicotine products in the past five days; and for those age 20-79 years, as < 100 cigarettes during their lifetime. "Occupational exposure" was defined as answering "yes" to questions about ever having workplace exposure to "mineral dust (i.e., dust from rock, sand, concrete, coal, asbestos, silica, or soil), organic dust (i.e., dust from fours, grains, wood, cotton, plants or animals), exhaust fumes (i.e., fumes from trucks, buses, heavy machinery, or diesel engines), or other fumes (i.e., vapors

from paints, cleaning products, glues, solvents and acids, or welding/soldering fumes) in any job." Survey participants were then asked about longest-held job, or current job if that was the longest-held job. Those who never worked or did not report a longest-held job were excluded from the study.

Study participants numbered 5,789; of these, 1,030 were excluded from spirometry for health or other reasons and 246, for poor quality spirometry. Overall the estimated prevalence of airflow obstruction was 13.7% (95% CI 12.4%-15.0%). Among ever-employed adults who reported any dust/fume exposure, 14.3% (95% CI 12.1-16.5) had airflow obstruction. For mineral dust exposure, prevalence of airflow obstruction was 15.3% (95% CI 12.1-18.6); for organic dust exposure, 15.6% (95% CI 13.0-18.2; for exhaust fumes, 17.7% (95% CI 14.5-21.0); and for other fumes, 15.4% (95% CI 12.5-18.3). Highest prevalence of airflow obstruction was observed for installation, maintenance, and repair occupations (22.1%, 95% CI 16.5-27.8), followed by construction, extraction work (20.7%, 95% CI 13.5-27.9). For office, administrative, and support occupations, prevalence was 10.3% (95% CI 6.2-14.5).

Smokers (n=1,972) had a significantly higher prevalence of airflow obstruction than never smokers. Among 2,188 *never smokers with no reported occupational exposures* (referent group), prevalence of airflow obstruction was 8.6% (95% CI 6.4-10.9). For *smokers who reported no occupational exposures*, prevalence of obstruction was 19.9% (95% CI 14.9-24.8), significantly higher than never smokers ($p < 0.0001$). For *smokers who reported any occupational exposure*, prevalence of airflow obstruction was 18.5% (95% CI 15.1-21.9), *vs.* 14.3% (95% CI 12.1-16.5) for *never smokers who reported any occupational exposure* ($p < 0.05$). For each occupational exposure group, prevalence of airflow obstruction was significantly higher among smokers than never smokers ($p < 0.05$). These findings add further support for an interactive effect between occupational exposures to a variety of VGDF and cigarette smoke on risk for COPD such that occupational-exposure-related risk is higher among smokers than nonsmokers.

CONCLUSIONS

COPD is a global public health problem. By 2020 it is expected to constitute the third leading cause of morbidity and mortality worldwide. In Ontario, COPD is a significant contributor to respiratory morbidity and mortality.

In the past, COPD has been attributed almost exclusively to cigarette smoking. Thanks in large part to Becklake and her illuminating review published in 1989, the paradigm has shifted.[20] We have learned that while smoking remains the predominant cause of COPD, a substantial proportion of the burden of COPD is attributable to occupational exposures to VGDF. The ATS has concluded that "The evidence is sufficient to infer a causal relationship between occupational exposures and development of COPD."[4] Multiple epidemiologic studies published in peer-reviewed journals have demonstrated associations that are statistically significant and consistent using different definitions of COPD and across different industries and occupations. Where measured, dose-response relationships have been observed. Experimental studies in animals have demonstrated biologic plausibility.

Published studies have also shown that occupational exposures act additively too synergistically with cigarette smoke in current or former smokers to increase the risk for COPD. NHANES data and other published studies indicate that certain industries and certain occupational exposures are associated with a significant increase in risk for COPD. At-risk occupations include mining, manufacture of motor vehicles and motor vehicle equipment, and construction.[29] Occupational exposures include mineral dusts, organic dusts, diesel exhaust, and other fumes.[39] In the same way that workplace exposures to VGDF and smoking interact to increase COPD risk over and above that associated with either exposure alone, it is likely that there is an interaction between single agents in the workplace on risk for COPD that is at least additive, although research remains to be done in this regard.[28]

Jaakkola in her editorial entitled "Smoke and dust get in your eyes: what does it mean in the workplace?" addresses an important clinical issue: the diagnosis of *occupational* COPD in current or former smokers.[41] Too often the fact of smoking precludes a determination that COPD is work-related. Either the physician fails to move beyond the smoking history to an occupational history in someone with COPD, or dismisses the occupational history as relatively unimportant in a smoker. As published data show and as the current paper describes, occupational exposures are an important and preventable cause of COPD in their own right. As Jaakkola correctly states: "It seems clear that being a smoker can no more mean that the individual does not have occupational COPD, as smokers appear to be at an even higher risk of developing work-related COPD than non-smokers." Smoking and exposure to VGDF in the workplace are separate risk factors for COPD and when combined there appears to be a synergistic effect. Along with the diagnosis come related issues of compensation for work-related COPD.

COPD is a preventable disease. As with all preventable diseases, recognition of the cause(s) is the first step toward reducing exposure to potentially toxic agents in order to prevent disease altogether, or to prevent worsening of disease in those already affected. Not only must we work to stop smoking, we must also work to maintain a safe and healthy workplace through substitution of non-toxic agents for toxic agents and where this is not possible, provision of adequate ventilation and proper respiratory protection.

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