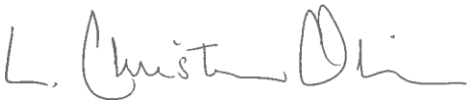
Occupational Health Clinics for Ontario Workers Inc.
Centres de santé des travailleurs (ses) de l'Ontario Inc.

Northern Region - Sudbury Clinic
84 Cedar Street, 2nd Floor
Sudbury, ON, P3E 1A5
Tel: (705) 523-2330
Fax: (705) 523-2606
1-877-817-0336
sudbury@ohcow.on.ca

IDIOPATHIC PULMONARY FIBROSIS: OCCUPATIONAL EXPOSURES AS A RISK FACTOR

Prepared by:



L. Christine Oliver, MD, MPH, MSc, FACPM

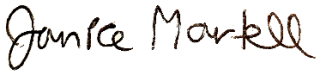
Medical Consultant, OHCOW

Occupational Hygiene Review:

Krista Thompson, MHSc, ROH, CRSP

Occupational Hygienist, OHCOW

Editorial Review:



Janice Martell

Occupational Health Coordinator, OHCOW

May 15, 2023

TABLE OF CONTENTS

IDIOPATHIC PULMONARY FIBROSIS: OCCUPATIONAL EXPOSURES AS A RISK FACTOR

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a member of the family of interstitial lung diseases known as idiopathic interstitial pneumonias (IIP). IPF is the most common of the IIPs.[1,2] Histologically it is characterized and defined by patchy distribution of fibrosis that appears to arise from the pleural surface; foci of subepithelial fibroblasts; and microscopic honeycombing.[1,3] This pattern is classified as "usual interstitial pneumonia", or UIP.[1,4]

The American Thoracic Society (ATS) and European Respiratory Society (ERS) have categorized IPF and idiopathic nonspecific interstitial pneumonia (NSIP) as "chronic fibrosing IP".[4] The histologic pattern of NSIP is different from that of IPF and is found in association with other conditions such as connective tissue disease (CTD), fibrotic hypersensitivity pneumonitis (HP), and drug toxicity. In addition to chronic fibrosing IP, major categories of IIP established by the ATS/ERS are smoking-related IP and acute/subacute IP.[5] Clinical manifestations and histologic and radiographic patterns differ. Multidisciplinary discussion (MDD), rather than surgical lung biopsy (SLB), is now considered the "gold standard" for diagnosis of IIP sub-types.[5,6]

Understanding of pathophysiologic mechanisms in IPF has shifted over time from inflammation as the primary mechanism to alveolar epithelial cell injury and impaired repair, with the production of profibrotic mediators, the activation of fibroblasts, and the differentiation of fibroblasts to myofibroblasts.[1,6,7] Consequently, treatment has moved away from anti-inflammatory immunosuppressive agents such as corticosteroids to antifibrotic agents such as nintedanib and pirfenidone. Neither is a cure; each has been shown to slow the rate of disease progression.

IPF is a chronic progressive interstitial lung disease, with poor prognosis. Rate of decline is variable, with median survival of 2.5 to 4 years.[2,8] The disease occurs most commonly in the sixth or seventh decade of life, with mean age at diagnosis of 66 years.[9] It is more common in males than females.

Incidence varies by country and by case definition.[7] A systematic review of 34 epidemiologic studies by Hutchinson et al revealed an estimated incidence of 3 to 9 per 100,000 person-years in Europe and North America; incidence rates were lower in South America and East Asia.[10] Using a broad case definition that excluded only cases with another interstitial lung disease (ILD) and a narrow case definition that excluded in addition cases without CT scan, lung biopsy, or bronchoscopy, Hopkins et al observed IPF incidence rates in Canada of 18.7 per 100,000 person-years and 9.0 per 100,000 person-years, respectively.[11] In Australia, age-adjusted estimated incidence rate was 11.2 per 100,000 person-years, calculated using data from the Australian Bureau of Statistics for the period 1997-2015 and data from the Australian IPF Registry.[12]

Utilizing a targeted literature search for global IPF incidence and prevalence for the period 2009 to 2020, Maher et al observed an estimated adjusted incidence of 0.75 (95% CI 0.28 - 2.00) per 10,000 in the U.S. and 0.93 (95% CI 0.54-1.60) per 10,000 in Canada.[13] The initial statistical model was adjusted for age, sex, study year, diagnostic criteria, study region/country, and population size. Maher et al included only studies with narrow case definitions that required confirmation of the IPF ICD-classification code with imaging studies and/or pathology, or review by trained staff.

IPF incidence and mortality rates appear to be increasing over time.[6,7,14] Strongman et al carried out a population-based cohort study of close-to-10 million patients in the UK.[14] Cases were identified using a primary care database. The purpose of the study was to examine IPF incidence, prevalence, and survival over the period 2000-2012. Annual incident rate ratios (IRRs) were estimated, adjusting for age, sex, and strategic health authority. IPF incident cases narrowly defined numbered 1,491 compared to 4,527 broadly defined. Overall annual incidence rates were 2.85 and 8.65 per 100,000 patient-years using narrow and broad case definitions, respectively. IRR increased over the study period by close to 80% for cases broadly defined: IRR 1.78, 95% CI 1.50-2.11. For cases narrowly defined, incidence declined: IRR 0.50, 95% CI 0.38-0.65.

In the U.S., IPF-attributable mortality increased by 9.85% over the period 2000 to 2017.[6] Mortality rate was 18.81 per 100,000 persons in 2000 and 20.66 per 100,000 in 2017 based on data from the U.S. National Statistics System. An even greater increase in IPF (cryptogenic fibrosing alveolitis (CFA)) mortality rate was observed in the UK over the period 1979 to 2016, from 1.66 per 100,000 persons to 8.29 per 100,000 persons.

Official ATS/ERS/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) clinical practice guidelines define IPF as "a specific form of chronic, progressive, fibrosing interstitial pneumonia of unknown cause."[15] The name belies the fact that a number of potentially causal associations have been identified for IPF. These include nonoccupational factors, and environmental and occupational exposures. Among the nonoccupational risk factors are age; male gender; family history; genetic mutations, including telomere-related gene mutations; certain viral infections such as Epstein-Barr and hepatitis C; microaspiration; CTD; and smoking.[7,15-17]

Occupational exposures associated with the development of IPF include metal and wood dusts, silica, and the broader category vapours, gases, dusts, and fumes (VGDF).[18] Other occupational exposures associated with increase in risk for IPF include farming, livestock, and animal and vegetable dusts.[19-21] Analysis of data collected as part of the Ontario Occupational Disease Surveillance System (ODSS) by the Occupational Cancer Research Centre (OCRC)revealed highest IPF risk among workers in gold and uranium mining and wood manufacturing and forestry services compared to all other workers in the ODSS.[22,23]

The purpose of this paper is to review IPF and etiologic factors that have been associated with the development of this disease. Focus will be on occupational and environmental exposures. Early diagnosis is key to longer survival; recognition of potential risk factors by practicing physicians and public and occupational health professionals is key to prevention.

DEFINITION

The ATS/ERS issued an international Consensus Statement in 2002 defining clinical features of the different and distinct IIPs.[4] The Consensus Statement was intended to standardize the classification of the IIPs and thereby reduce confusion and aid in diagnosis and medical and scientific research. The clinical features defined are clinical presentation, respiratory symptoms, and radiologic and pathologic characteristics. In 2013, the ATS/ERS met again to update the classification of the IIPs.[5]

IPF is the most common of the IIPs, accounting for approximately 60% of cases.[24] It is a rare disease.[12] By definition IPF is idiopathic. Incidence increases with increasing age, with age at onset typically greater than 50 years.[5] IPF occurs more commonly in males. Clinical symptoms in the earlier stages of the disease are respiratory: dry cough and shortness of breath. Pulmonary function tests and

chest X-ray may be normal. As the disease progresses, as it inevitably does, a restrictive defect develops, with reduction in forced vital capacity (FVC) and total lung capacity (TLC). Impairment in gas exchange occurs, with reduced single breath diffusing capacity for carbon monoxide (DLCO) and hypoxemia.

A UIP pattern of fibrosis is an integral part of the definition of IPF.[4,5] All cases of IPF have the UIP pattern; not all cases of interstitial lung disease with UIP pattern are IPF. A UIP pattern is determined on the basis of high-resolution chest CT scan (HRCT) and/or histopathology. Characteristically, HRCT shows reticular opacities, traction bronchiectasis, and honeycombing. There may be architectural distortion related to fibrosis. These changes are seen predominantly at the lung bases and the periphery of the lungs.

UIP is characterized histopathologically by its patchy distribution, with areas of normal or almost normal lung tissue adjacent to areas of established fibrosis and less-well-established fibroblastic foci.[5,24] The latter are believed to represent areas of recent lung injury. Honeycombing is present, both macroscopically and microscopically. Fibrotic changes are predominantly subpleural and paraseptal in location. Chronic inflammatory changes are limited to areas of established fibrosis and are minor relative to other interstitial lung diseases. A surgical lung biopsy (SLB) is required for the definitive histopathologic diagnosis of IPF.[5]

PATHOGENESIS

Scientific thinking about the pathogenesis of IPF has evolved considerably over the past four to five decades (Table 1). Pathogenesis was attributed to chronic inflammation early in the history of IPF.[1,24] However, the degree of inflammation did not correlate well with the severity of the pulmonary fibrosis nor was there a clinical response to treatment with anti-inflammatory or immunosuppressive drugs. As a result, the belief that inflammation was the principal mechanism in IPF pathogenesis was discarded and new paradigms were developed to explain the pathogenesis of IPF.[3,7,24]

Strieter and Mehrad proposed the paradigm of alveolar epithelial injury followed by impaired repair, with these steps being integral to the process:[25]

1. Loss of the integrity of the basement membrane (BM) of the alveolar-capillary junction where gas exchange in the lungs occurs;
2. Failure of re-epithelialization and re-endothelialization of alveolar and capillary BMs, respectively;
3. Consequent destruction of normal lung architecture and development of fibrosis;
4. Further lung injury caused by persistence of antigens/irritants responsible for BM injury; and
5. Transition of epithelial to mesenchymal cells and influx of bone marrow progenitor cells in the form of fibrocytes.[25]

Cytokine growth factors and other cellular and molecular mediators are important participants in the process. The anatomical target is the respiratory lobule consisting of a terminal bronchiole, a respiratory bronchiole, alveolar duct, and alveolus on one side, and alveolar capillary and pulmonary venule on the other, held together by the alveolar-capillary BMs and extracellular matrix of the lung interstitium.

Wolters et al have proposed an overlapping paradigm, with the lung epithelium playing a critical role.[3] A three-stage process is proposed: "predisposition, activation, and progression."

1. Predisposition: Predisposing factors are both intrinsic and extrinsic.
   a. Intrinsic predisposing risk factors include ageing, male gender, genome, and telomere shortening.
   b. Extrinsic predisposing factors include environmental insults from inhalational and non-inhalational agents.
2. Activation: Activation occurs in a predisposed individual as a result of accumulated environmental insults, causing lung epithelial cell injury and a cascade of events similar to those described by Strieter and Mehrad.[3,25]
3. Progression: The final step is progression, with replacement of normal lung architecture with remodelled fibrotic tissue.

In this context, Trethewey and Walters consider the role of occupational and environmental exposures in pathogenesis.[7] Among potentially causal exposures cited are organic dusts, metal and wood dusts, asbestos, and ambient particulate matter. The ambiguity of identified occupational and environmental exposures as causal risk factors for "idiopathic" pulmonary fibrosis is recognized and attributed in part to incomplete occupational and environmental exposure histories.

DIAGNOSIS

In 2011 the ATS/ERS/JRS/ALAT issued an official statement setting forth evidence-based guidelines for the diagnosis and management of IPF.[26] These were updated in 2018 and, most recently, in 2022 .[15,27] The guidelines are intended for application to patients who are "clinically suspected of having IPF"; namely a patient with or without symptoms who has newly-detected bibasilar pulmonary fibrosis of apparently unknown cause on chest X-ray or HRCT, crackles at both lung bases on physical exam, and age in the range of 60 years or older. HRCT is a necessary first step in application of the guidelines as findings determine subsequent recommendations. In addition to aiding physicians in the diagnosis of IPF, by establishing a framework the guidelines are useful in clinical and epidemiologic research.

Diagnostic criteria for IPF set forth in the 2018 ATS/ERS/JRS/ALAT clinical practice guidelines and reiterated in the 2022 guidelines are as follows:

1. Exclusion of other known causes of ILD, AND
2. A UIP pattern of fibrosis on HRCT, OR
3. Specific combinations of HRCT patterns and histopathology in cases with probable or indeterminate UIP patterns on HRCT.[15]

A UIP pattern on HRCT is defined as "honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis" that is subpleural and predominantly basal in location; although heterogeneous distribution is often observed.[15] Guidelines published in 2022 clarify with regard to the size of the airways most often involved in honeycombing: histopathologic-HRCT correlations show that honeycombing and bronchiolectasis are closely related in that honeycombing represents bronchiolar cysts that form in association with "collapse of fibrotic alveolar septa and dilatation of terminal airways", or bronchioles.[27]

A consistent clinical picture and a UIP pattern on HRCT are considered sufficient for a diagnosis of IPF if criterion #1 is satisfied. To satisfy criteria for diagnosis, a probable or indeterminate UIP pattern on HRCT would require a definite or probable UIP determination on histopathology: "1) patchy dense fibrosis with architectural distortion (i.e., destructive scarring and/or honeycombing); 2) a predilection for subpleural and paraseptal lung parenchyma; 3) fibroblastic foci; and 4) the absence of features that suggest an alternative diagnosis." [15,27]

Consistent histopathology was once considered the gold standard for the diagnosis of IPF, and SLB was required for the definite histopathologic diagnosis of IPF.[5] The 2018 guidelines strongly recommended against performing a SLB in cases with UIP pattern on HRCT; whereas in 2011 the guidelines simply stated that SLB is not required under these circumstances.[15] The 2022 guidelines do not change the 2018 guidelines regarding use of SLB in the diagnosis of IPF.[27] In 2011 MDD was recommended as a first step before SLB, and in 2018 suggested in most cases for which diagnosis is uncertain. [15,26-29] Cellular analysis of bronchoalveolar lavage (BAL) is suggested when the HRCT pattern is anything other than UIP; measurement of serum biomarkers is not recommended.[15]

To exclude other known causes of ILD, the guidelines recommend a detailed occupational and environmental exposure history, a history of medication use, and serologic testing for CTD. Other risk factors to be investigated are the following: smoking; family history (FH) of ILD; gene mutations, including telomere-related mutations; gastroesophageal reflux (GER) and microaspiration; certain drugs; and certain viral infections such as hepatitis B and Epstein-Barr virus. These risk factors are discussed below, with the exception of drugs and viral infections which are beyond the scope of this paper.

ETIOLOGY – NONOCCUPATIONAL RISK FACTORS

Family History

Familial occurrence has been observed among IIPs.[1,30-32] Familial and sporadic IPF are virtually indistinguishable clinically, with the exception that familial IPF tends to occur at an earlier age.[5,32] Genetic factors play a role in both.[15,33,34] Familial interstitial pneumonia (FIP) has been defined as IIP in which 2 or more first-degree relatives are affected.[1,31,32] FIP is inherited as an autosomal dominant and accounts for 2% to 20% of cases of IIP overall, and 0.5% to 2% of cases of IPF.[31,32] The extent to which so-called familial IPF cases may reflect geographic proximity of the family to a toxin source, as has been observed with beryllium for example, or the carry-home of an occupational toxin across generations, as has been observed with asbestos, has not been investigated to our knowledge.

Garcia-Sancho et al conducted a case-control study of consecutive IPF cases at the National Institute of Respiratory Disease in Mexico during the period 2007 to 2009. [30] One hundred cases were matched with 263 controls on age, sex, ethnicity, and place of residence. Structured questionnaires were administered to obtain information about potential risk factors such as FH, environmental and occupational exposures, cigarette smoking, GER, and type II diabetes. In multivariate regression analysis, FH emerged as the strongest risk factor for IPF: parent/sibling with IPF adj. odds ratio (OR) 6.1 (95% confidence interval (CI) 2.3-15.9), $p<0.0001$. The following variables also achieved statistical significance: former smoker adj. OR 2.5 (95% CI 1.4-4.6), $p=0.003$); occupational exposure to VGDF adj. OR 2.8 (95% CI 1.5-5.5), $p=0.002$; and GERD adj. OR 2.9 (95% CI 1.3-6.6), $p=0.007$.

Genetic Variants in Sporadic and Familial IPF

There is considerable overlap between clinical and genetic characteristics of sporadic and familial IPF. Fifteen to 20% of IPF cases report a FH of the disease in close relatives.[34] Common genetic mutations have been described in telomerase and surfactant protein genes, among others. These appear to influence susceptibility to IPF, pathogenesis and survival, and treatment.[34-39] The strongest known genetic risk factor for sporadic and familial IPF is the mucin 5 B (MUC5B) promoter variant (rs35705950). Genome-wide association studies (GWAS) of cases of IPF and interstitial lung abnormalities (ILA) defined on the basis of chest imaging studies revealed the MUC5B promoter variant to be the dominant variant in both IPF and ILAs; distinct genetic variants not associated with IPF were observed for ILAs.[35]

Key to the pathogenesis of IPF are host defense mechanisms and cell senescence, or ageing.[33] The MUC5B genotype appears to play an important role in IPF risk as well as survival, due in part to its role in the lung's defense against alveolar epithelial cell injury.[1,34,36] In a large retrospective study of all-cause mortality in IPF patients in Europe, the U.S., and Canada, Peljto et al observed improved survival in patients who carried the MUC5B minor allele (T). In other words, IPF patients whose genotype was GT or TT lived significantly longer than those with GG genotype.[36] Paradoxically, the same MUC5B polymorphism associated with longer survival is also associated with increased risk for disease. Why is not yet clear.

Short telomeres and telomerase mutations, on the other hand, are associated with more rapid IPF progression and shorter life span.[16, 17, 38, 39] Telomeres are nucleotide sequences that limit chromosome shortening during replication by capping the ends of chromosomes. Telomeres shorten with ageing. As telomeres shorten the chromosome becomes vulnerable to DNA damage with activation of a response that results in cell death.[16] IPF is the most common ILD associated with short telomeres and telomere-related mutations, found in greater than 30% of cases of familial IPF and 10% of cases of sporadic IPF.[16] Normal lung function requires the constant replacement of alveolar epithelial cells; so that plentiful reserves are needed. Short telomeres and telomerase mutations accelerate cell death and limit these reserves, thus playing a key role in the pathogenesis and progression of IPF.

Telomerase is an enzyme that protects against telomere shortening by adding telomere repeats to the end of the chromosome.[38] Telomerase-related mutations interfere with this protective maintenance activity, and are associated with more rapid progression and reduced survival in IPF patients and perhaps in patients with other ILDs as well.[39] Among the telomerase-related mutations identified as important in IPF are TERT, TERC, and PARN.

Gastroesophageal Reflux

Epidemiologic data have shown associations between GER and IPF.[15,30] The case-control study by Garcia-Sancho et al showed a close-to-threefold increase in risk for IPF in patients with GER.[30]

GER has not been established as a causal factor in the development of IPF.[40] But there is indirect and more direct evidence of an association between GER and IPF. Indirect evidence comes in the form of studies showing stabilization or improvement in the clinical condition of IPF patients treated with proton-pump-inhibitors or H2-antagonists.[40] More direct evidence comes in the form of a case-control study by Tobin et al showing lower esophageal pH and longer duration exposure to pH < 4.0 in 17 patients with IPF, compared to 8 controls with other types of ILD.[41] Pepsin, a marker of microaspiration, was found in sputum and BAL of cases. Lee et al observed pepsin and elevated percentages of

neutrophils in white blood cell counts in the BAL of IPF patients with acute disease exacerbation compared to patients in stable condition.[42]

These findings suggest microaspiration as a causal factor.[40] The most likely mechanism is injury to lower respiratory tract epithelial cells caused by exposure to acid, pepsin, bile acids, and other constituents of gastric juice. Epithelial cell injury and impaired repair are important in the pathogenesis of IPF.

ETIOLOGY – OCCUPATIONAL EXPOSURES AND IPF

GENERAL

Over the past several decades occupational exposures have emerged as a substantial contributing factor in the development of IPF in published scientific literature (Table 2).[7,8,18] Epidemiologic studies have shown variation in strength of association, but consistency overall across authors and geographic areas of investigation for specific occupational exposures.

In their examination of the occupational burden of nonmalignant respiratory diseases (NMRD), Blanc et al conducted a search of largely population-based literature for studies of associations between occupational exposures and certain respiratory diseases, including IPF.[18] For IPF, the pooled estimate for population-attributable fraction (PAF) derived from all studies considered was 26% (95% CI 10-41%), leading Walters to conclude that "occupational factors contribute substantially [to risk for IPF], and explain one quarter of the burden of IPF."[8]

With regard to specific occupational exposures, Blanc et al observed the following:[18]

AGENT	POOLED ODDS RATIO	95% CONFIDENCE INTERVAL
VGDF	2.00	1.2-3.2
Metal Dusts	2.00	1.3-3.0
Wood Dusts	1.70	1.3-2.2
Silica	1.70	1.2-2.4
Agricultural Dusts	1.60	0.8-3.0

In interpreting the published literature on occupational exposures and IPF, several factors are important to consider. These include study design, case definition, the potential for misclassification of disease, and the source of information about occupational exposures.

Study Design. Much of the data showing associations between workplace exposures and IPF comes from case-control studies. While cohort studies arguably provide more robust data, in the case of a rare disease outcome, case-control studies are a practical and reliable alternative despite certain potential weaknesses such as poor subject memory for remote exposures.

Case Definition. The definition of IPF is based upon accepted diagnostic criteria. These criteria evolve and change over time. In 2000 the ATS/ERS published an international consensus statement defining IPF as follows: SLB showing UIP for the definite diagnosis of IPF; exclusion of other known causes of ILD; abnormal PFTs showing evidence of restriction and/or impaired gas exchange; and abnormal chest X-ray and/or HRCT showing bibasilar reticular abnormalities with minimal ground glass opacities.[9] In 2018 the ATS/ERS/JS/ALAT published an update of the 2000 criteria and their 2011 criteria for the diagnosis of IPF.[15,26] Compared to 2011 the changes were minor: in cases with an HRCT pattern of

UIP, SLB is not recommended, and MDD is suggested for clinical decision making. Compared to 2000, however, the changes were more substantial. The current guidelines require HRCT pattern of UIP for definite IPF diagnosis; SLB is no longer recommended in this circumstance.[15] Chest X-ray is not an acceptable imaging modality and abnormal PFTs are no longer required.

Would these differences in diagnostic criteria affect outcome in epidemiologic studies? Hopkins et al observed a doubling of IPF incidence rate in Canada using a broad case definition vs. a narrow one; so that the possibility exists and illustrates the importance of paying attention to criteria used for case definition in interpreting epidemiologic studies.[11]

***Misclassification of Disease*.** The classification scheme for IIPs is complex, as are the clinical guidelines for diagnosing IPF. Both factors increase the potential for misclassification of disease. An example of such misclassification is provided by a case-cohort study of 60 IPF patients conducted by Morell et al.[43] The original diagnosis was made using the 2000 ATS/ERS criteria.[9] The patients received clinical follow-up during the period 2004 to 2009. The diagnosis of IPF was upheld in 46 patients with the application of 2011 ATS/ERS/JRS/ALAT guidelines.[26] Additional data were collected on these 46 patients, including serum-specific IgGs. Twenty-nine had lung tissue available for histopathologic review. Of the 46, 20 (43%) were determined to have chronic hypersensitivity pneumonitis (CHP). Of these, 16 had histopathology consistent with CHP, not IPF.

Historical Recall. For epidemiologic studies of occupational disease, occupational hygiene data on workplace exposures are often lacking. Occupational histories provide the primary source of information about historical exposures. Memories are faulty. Fortunately, we have methods to backstop faulty memory. These include the use of standardized questionnaires to collect detailed lifetime work histories and the use of a job-exposure matrix (JEM) to analyze and, where possible, quantify exposures.

Summary. Despite these potential weaknesses in study design and data collection, in the case of IPF there is consistency of findings across studies that supports reliability overall, with significant associations being reported between IPF and the following occupational exposure categories: organic dusts (agriculture, livestock, vegetables, birds); metal dusts; wood dusts; inorganic dusts (silica, asbestos); and VGDF.

SPECIFIC

Organic Dust

Organic dust is a recognized cause of hypersensitivity pneumonitis (HP), which can present as chronic fibrotic ILD (fCHP). Organic dust is less-well recognized as a risk factor for IPF. Blanc et al observed an estimated PAF of 4% (95% CI 0-12%) for agricultural dusts; the estimated pooled OR was 1.6 (95% CI 0.8-3.0).[18]

Scott et al conducted a case-control study of chronic fibrosing alveolitis (CFA) (synonymous with IPF) in Nottingham, UK.[44] Forty cases were selected from a CFA registry and compared to 106 age- and sex-matched controls randomly selected from the patient lists of the case's general practitioner. A questionnaire was mailed to the home of each participant to obtain information on places of residence; current and prior work and workplace exposures; animal exposures at work and at home; and smoking. Statistically significant associations were observed for exposure to cows, with large confidence intervals reflecting small numbers (OR 10.89, 95% CI 1.24-96.0).

In 2000 Baumgartner et al published the results of a multicentre case-control study of occupational and environmental exposures as risk factors for IPF.[20] Two hundred forty-eight cases age 20-75 years were diagnosed at 16 referral centres between January 1989 and July 1993, and compared to 491 randomly selected controls matched on age, sex, and area of residence. Diagnosis of IPF was based on clinical presentation and one or more of the following, where available: open lung biopsy, transbronchial (TB) lung biopsy, BAL, or chest CT scan. A UIP pattern was not a diagnostic criterion. Cases with an occupational history of exposure to an agent(s) associated with an IPF-like clinical picture and a history of exposure to an agent(s) associated with HP together with positive serum-specific IgG were excluded.

Information on demographic variables and smoking, and 33 job activities, 14 occupational exposures, and 12 hobbies, was collected by telephone interview.[20] A semi-structured interview queried all jobs held for 6 months or more. Jobs were coded using the Standard Industrial Classification (SIC) and the Standard Occupational Classification (SOC) systems. In multivariate analysis adjusting for age and other exposure variables, significant associations were observed for the following: smoking, OR 1.8 (95% CI 1.2-2.7); raising birds, OR 4.1 (95% CI 1.3-13.4); and livestock, OR 2.2 (95% CI 1.0-4.7). Stratification of exposure by duration < 5 years vs. $\geq$ 5 years revealed positive dose-response relationships in multivariate analysis, with significant associations observed for duration of 5 or more years for the following: livestock, OR 3.3 (95% CI 1.3-8.3); raising birds, OR 7.2 (95% CI 2.0-28.6); and vegetable/animal dust, OR 4.5 (95% CI 1.0-10.8).

Ekstrom et al carried out a population-based case-control study of severe pulmonary fibrosis (PF) in Sweden during the period February 1997 to April 2000.[45] Cases were selected from a national registry of patients on long-term oxygen therapy (LTOT). A questionnaire designed to obtain information about smoking and occupational exposures was mailed to 171 cases and 719 randomly selected controls. Occupational and domestic exposures to birds were queried. Of the 171 cases of PF, 137 were designated as IPF based on a review of their medical record by 2 pulmonary medicine specialists. PF risk was increased significantly with occupational exposure to birds and wood dust. For IPF the increase in risk was not significant, with OR 1.3 (95% CI 0.6-2.8). For PF and IPF, an interactive effect was observed for smoking, gender, and occupational exposure NOS, as well as occupational exposure to birds (p=0.021) and wood dust (p=0.023), with males being at greater risk.

Gustafson et al observed increased risk for occupational exposure to organic dust in a case-control study of a group of IPF patients in Sweden.[46] Methods used were the same as those used by Ekstrom et al.[45] Potential cases were selected from 241 registrants in the Swedish Oxygen Register with a diagnosis of PF. A subgroup of 140 patients with IPF was identified. One hundred fourteen (81.4%) were male.

Exposure $\geq$ 5 years prior to diagnosis was required for cases to be classified as exposed. Risk for any occupational exposure (organic dust, wood dust, inorganic dust, metal dust) was increased among all cases with PF (OR 1.6 (95% CI 1.06-2.37), n=123) but not among the subset of cases with IPF (OR 1.1 (95% CI 0.71-1.72), n=86), adjusting for sex, birth year, year of diagnosis, and smoking. Risk for exposure to organic dust was increased for PF (OR 1.7 (95% CI 1.04-2.70), n=54). Increased risk for exposure to birds was observed for IPF: OR 2.7 (95% CI 1.00-7.06).

Kim et al conducted a hospital-based retrospective case-control study of occupational and environmental risk factors for chronic fibrosing IIPs in South Korea.[47] Cases included IPF and NSIP. Patients diagnosed with IPF or NSIP in the respiratory centre of a university hospital from January 2011

to December 2014 were recruited into the study. Diagnosis was made on the basis of ATS/ERS consensus classification, with consistent histopathology on SLB and/or consistent pattern on HRCT.[4] Diagnosis was made at MDD. Controls were selected from healthy patients seen for annual health examinations at the same institution. Selection was random and matching was done on the basis of age and sex. Ninety-two cases and 92 controls were selected to participate in the study. Of the 92 cases, 70 were IPF and 22, NSIP.

Occupational and environmental exposure information was collected by a trained occupational hygienist and industrial nurses by telephone using a structured questionnaire. Thirty-four job activities and 22 specific exposures were queried and coded using Standard Industrial (SIC) and Standard Occupational (SOC) Classifications. Of specific interest were metal dust, stone/silica/sand, organic solvents, wood dust, organic dust, and inorganic dust as exposure categories. A greater than fourfold increase in risk was observed among IPF cases who reported work in agriculture: OR 4.50 (95% CI 1.25-16.23), n=16.

Paolocci et al observed a statistically significant association between UIP on HRCT and/or histopathology and self-reported work as a farmer, veterinarian, or gardener (OR 2.73 (95% CI 1.47-5.10)) in their case-control study of IPF in Italy.[21] The 69 UIP cases were patients seen at Perugia University Hospital in Umbria during the period January 2010 to December 2013. Definition of "exposure" was work at a given job for $\geq$ 5 years; for cases, latency of $\geq$ 5 years was required. Cases were compared to 308 controls randomly selected from the Umbria region. Information was collected via telephone administration of an extensive questionnaire.

Thirty cases (44%) vs. 51 controls (18.4%) worked as farmers, veterinarians, or gardeners ($p<0.01$).[21] Exposures were to organic dusts and aerosolized particulate matter from feed grains, animal bedding, and fecal material. Adjusting for age, gender, and smoking, OR for exposure to organic dust was increased more than twofold: OR 2.4 (95% CI 1.3-4.3). Duration of work for > 20 years was associated with an increase in UIP risk over and above that associated with lesser durations of exposure, suggesting a dose-response relationship: 1-9 years, OR 3.32 (95% CI 1.06-10.33); 10-19 years, OR 3.41 (95% CI 1.30-8.95); > 20 years, OR 5.01 (95% CI 2.55-9.84).

Organic dust is a risk factor for HP and IPF. Fibrotic CHP bears clinical resemblance to IPF. Histopathology and HRCT are helpful in distinguishing the two, with histology typically showing granulomas in CHP.[48,49] Survival is shorter for IPF compared to CHP, with life expectancy of about 3 years following diagnosis. De Sadeleer et al explored the issue of prognosis further, comparing survival in the following groups: 171 patients with IPF and no history of exposure to birds/moulds (group A); 73 patients with IPF and a history of exposure to birds/moulds (group B); and 49 patients with CHP (group C).[50] Detailed occupational, recreational, and domestic histories were obtained in the clinical setting from each patient diagnosed with either IPF or CHP. IPF has been associated with bird exposure; diffuse pulmonary fibrosis (DIF), with mould/mildew exposure.[19,45. 51]

The study was carried out at University Hospitals Leuven in Leuven, Belgium, with enrollment of patients during the period April 2000 to June 2016, and follow-up to August 2016. Subjects were assigned to one of the 3 diagnostic groups at MDD. Mortality was assessed using a multivariate Cox proportional hazards model, adjusting for age, gender, ever-smoking, treatment, and baseline FVC.

Median survival for group A was 43 months compared to 84 months for group B, and 156.8 months for group C. Mortality rate was significantly lower in group B compared to group A (hazard ratio

(HR) 0.48, p=0.002) and in group C compared to group B (HR 0.47, p=0.037). In the multivariate analytical model comparing mortality rates in groups A and B, mould/bird exposure emerged as a significant independent variable contributing to better survival in group B, with HR 0.60 (95% CI 0.37-0.97), p=0.037. Other significant variables in the model were age (HR 1.03 (95% CI 1.00-1.06), p=0.030), antifibrotic therapy (HR 0.36 (95% CI 0.23-0.55), p< 0.001), and baseline FVC (L) (HR 0.73 (95% CI 0.55-0.96), p=0.027).

Each of the 3 groups was screened for markers that typically distinguish CHP from IPF. These included ever-smoker (group B 79.5% vs. group C 46.9%, p<0.001); family history of ILD (group B 23.3% vs. group C 6.4%, p<0.001); serum-specific IgGs (group B 43.9% vs. group C 66.7%, p=0.032); BAL lymphocytosis (group B 8.8 (± 8.4) vs. group C 41.9 (± 17.6), p<0.001); and characteristic findings on CT scan. These results indicate that any misclassification of CHP as IPF would have been minor and suggest that IPF associated with bird exposure may have a better prognosis than IPF associated with no or other exposure.

Metal Dust

Occupational exposure to metal dusts has been associated with increased risk for IPF in a number of epidemiologic studies.[18,21,44] Based on their review of 12 published studies with 9 risk estimates, Blanc et al computed a pooled OR of 2.0 (95% CI 1.3-3.0) for metal dusts and IPF; with an estimated pooled PAF of 8% (95% CI 4%-13%).[18] Baumgartner et al in their multicentre case-control study observed a significant increase in IPF risk associated with occupational exposure to metal dust, with OR 2.3 (95% CI 1.1-4.8) in males.[20] Increase in risk was significant only for those with duration of exposure ≥ 5 years: OR 2.2 (95% CI 1.1-4.7).

In their case-control study of 40 cases of CFA selected from a case registry in Nottingham, UK, Scott et al observed an elevenfold increase in risk for metal dust exposure, with wide confidence intervals reflecting small numbers: OR 10.97 (95% CI 2.30-52.4), p<0.001, n=12.[44] Jobs with potential metal dust exposure were metal worker, fitter, or machinist; machine (e.g., lathe) operator; and welder or galvanizer.

In the case-control study by Paolocci et al, 8 cases (11.6%) compared to 6 controls (2.2%) gave a history of work in the metallurgical and steel industry (p=0.02).[21] UIP risk was increased for the group as a whole and in males: OR 4.80 (95% CI 1.50-15.33) and OR 4.76 (95% CI 1.50-15.15), respectively. Longer duration of work was associated with increased risk of disease, adjusting for age, gender, and smoking:

EXPOSURE DURATION	ODDS RATIO	95% CONFIDENCE INTERVAL
None	1.00	
1-9 Years	3.32	1.06-10.33
10-19 Years	3.41	1.30-8.95
≥20 Years	5.01	2.55-9.84

Self-reported history of occupational exposure to metal dust or fumes was associated with a close-to-fourfold increase in risk for UIP, adjusting for age, gender, and smoking: OR 3.8 (95% CI 1.2-12.2), n=9. By definition, self-reported exposure was an exposure or work at an at-risk occupation for ≥ 5 years and occurring ≥ 5 years prior to diagnosis of UIP pattern on chest CT scan.

In a case-control study of CFA in the Trent region of the UK, Hubbard et al observed a significant increase in risk for occupational exposure to metal dust.[52] Lifetime occupational histories were collected by postal questionnaire and verified by telephone interview from 165 cases and 408 controls. Potential cases were selected from 4 teaching and 5 general hospitals based on local diagnostic registers, inpatient coding data, and lung function test results; and cases chosen based on clinical record review. Selection criteria were consistent histology on SLB; or bibasilar crackles on physical exam, ILD on chest X-ray, exclusion of other likely cause of ILD, and restriction or low DLCO on PFT or consistent HRCT scan if restriction was lacking. Prevalent cases were those present at the start of the study and incident cases, new cases identified during the study period October 1992 to March 1994.

Cumulative dust exposure was calculated in work-years with 1 work-year defined as 8 hours of dust exposure/day x 1 year. Skin prick tests and measurement of serum IgE and autoimmune antibody titers were carried out to exclude atopy and CTD as potential confounders. Multivariate logistic regression analysis was adjusted for age, gender, and smoking.

Of 218 cases, 32 (14.7%) reported occupational exposure to metal dust both on the questionnaire and at the follow-up interview. The most common occupation was machine operator, including work as a lathe turner and metal polisher. Adjusting for smoking and wood dust exposure, metal dust exposure was significantly associated with IPF whether data were collected by questionnaire, interview, or a combination of the two: OR 1.68 (95% CI 1.07-2.65); OR 2.22 (95% CI 1.26-3.91); and OR 2.59 (95% CI 1.13-5.90), respectively. Significant associations were observed for brass, lead, and steel. A positive exposure-response relationship was observed, with OR 1.11 (95% CI 1.06-1.16) per work-year exposure, $p<0.001$. Minimum latency was $\geq$ 5 years; median latency, 47.5 years. Estimated attributable risk varied by method of data collection: questionnaire 10.3%, interview 13.4%, and combined 12.5%. In concluding, the authors state, “Although the cause of most cases of CFA remains unexplained our findings challenge the concept that this is a disease of unknown aetiology.”

To further investigate the observed association between IPF and metal dust exposure, Hubbard et al conducted a proportional mortality (PMR) study of IPF among employees of Rolls-Royce Plc at 5 sites in the UK.[53] Information on cause of death was obtained from death certificates held in pension fund records of employees. CFA was defined as a recording of cryptogenic fibrosing alveolitis, fibrosing alveolitis, or idiopathic pulmonary fibrosis anywhere on the death certificate. Controls were randomly selected from death certificates with no mention of fibrotic lung disease. PMR was estimated by indirect standardization for age and sex using national mortality data for 1986. Cohort PMR for lung cancer was also calculated as an indicator of whether prevalence of smoking was higher in the study cohort.

Occupational exposures were estimated by an occupational hygienist working for Rolls Royce using personnel employment records. Risk of death from CFA in metal-exposed workers was estimated according to duration of exposure, adjusting for sex and for age at death in logistic regression analysis.

Fifty-five CFA deaths were identified; occupational records were located for 40% of cases and 38% of 621 controls. Risk was elevated for sheet metal workers only, with OR 21.0 (95% CI 3.47-141.9). Median duration of exposure was 9.3 years for cases and 5.4 years for controls. Risk for death from CFA was related to duration of exposure: OR 1.71 (95% CI 1.09-2.68) per 10 years exposure, $p=0.02$. Risk of death from lung cancer was not increased.

Miyake et al observed a significant association between occupational exposure to metal dust and IPF in a hospital-based case-control study in Japan.[54] Cases were selected using guidelines set forth by the ATS/ERS in 2002.[4] A self-administered questionnaire was used to obtain the following information: longest-held job; exposure to one or more of 13 occupational agents for $\geq$ 10 hours per week; domestic exposure to mould or pets; and town or city of residence. Jobs were stratified into 11 major groups.

One hundred two IPF cases were compared to 59 controls with acute pneumonia or common cold. Over 90% of cases and controls were male. Smoking was defined by status (never, former, current) and pack-years. Multiple logistic regression analysis was adjusted for age, sex, and residence. The only significant association observed for job group was a negative association with clerical work. For occupational agents, significant positive associations were observed for any dust and metal dust: OR 5.61 (95% CI 2.21-17.89), n=33, and OR 9.55 (95% CI 1.68-181.12), n=12, respectively. Associations with domestic exposures were not significant.

Using multiple cause of death data from the National Center for Health Statistics, the U.S. National Institute for Occupational Safety and Health (NIOSH) conducted a study of IPF mortality in the U.S. for the period 1999 to 2003.[55] Industry-specific PMRs were calculated for 19 states using 3-digit Census Industry Codes and adjusting for age, sex, and race. Mortality odds ratios (MOR) were estimated using matched case-control logistic regression analysis. Cases were defined as those whose death certificates included IPF (ICD-10 code J84.1) as the underlying or a contributing cause of death. Controls were those whose death certificates did not include codes for any ILD or for sudden death from injury, poisoning, or other external cause.

The age-adjusted mortality rate for IPF for the study period was 75.7 per million; it increased significantly over the period of the study (r^2=0.98, p<0.001). Elevation in IPF PMR was observed for the following industries: wood buildings and mobile homes (OR 4.5 (95% CI 1.2-11.6)); metal mining (OR 2.4 (95% CI 1.3-4.0)); and fabricated structural metal products (OR 1.9 (95% CI 1.1-3.1)). IPF MOR was elevated for each of these industries, providing confirmation of PMR analyses: MOR 5.3 (95% CI 1.2-23.8); MOR 2.2, (95% CI 1.1-4.4); and MOR 1.7 (95% CI 1.0-3.1), respectively. The authors concluded that IPF PMRs in these industries with likely occupational exposures to metal or wood dust were among the highest in the U.S.

Iwai et al conducted a case-control study of associations between IPF and occupational exposures in Japan.[56] Cases were selected from the Annuals of the Pathological Autopsy Cases in Japan (APACJ) covering the period 1974 to 1985; controls were randomly selected from the same records. The number of IPF cases was 1,311.

Job categories included metal and iron production workers, miners, shipbuilders, and wood production workers. Because of small numbers, dust-related and solvent-vapour-related jobs were combined into a single exposure group. Job categories for which prevalence was increased are the following: metal production worker; wood production worker; painter; and laundry worker, barber, beautician (p<0.001). Compared to 2 groups of unexposed controls and 1 group of respiratory disease controls, prevalence of “occupational exposures” was significantly elevated in 266 IPF cases compared to unexposed controls (OR 2.80 (95% CI 1.09-7.22), p<0.05).

The authors also conducted a case-control study of living IPF cases in Japan. Eighty-six IPF cases were selected from 12 districts based on clinical findings, chest radiograph or CT abnormalities, PFT

results, and the exclusion of known causes of pulmonary fibrosis. Two healthy controls and 1 control with non-IPF respiratory disease from the same hospital were selected for each case. Matching was done on age, sex, and residential area. Information was obtained from questionnaires administered by experienced interviewers. Compared to hospital controls, relative risk (RR) for IPF was elevated for cadmium, chromium, lead, zinc, "metal", and "mine" (RR 1.37 (95% CI 1.08-1.73), p<0.01). Compared to healthy controls, RR was elevated for tobacco (RR 2.94 (95% CI 1.37-6.30), p<0.01); metals and mining (RR 1.34 (95% CI 1.14-1.59), p<0.01); agricultural area (RR 3.01 (95% CI 1.29-7.43), p<0.05); agricultural chemicals (RR 3.32 (95% CI 1.22-9.05), p<0.05); and urban and polluted air (RR 3.33 (95% CI 1.26-8.79), p<0.05).

Occupational histories for autopsy cases were nonspecific with regard to job but suggested exposure to dusts and vapours, particularly metal dust and solvent vapours. The more specific histories obtained from living cases support metal dust exposure for IPF autopsy cases. These histories also provide support for associations between occupational exposure to organic dusts and IPF observed by others in subsequent studies.[20,21,50]

Wood Dust

Occupational exposure to wood dust has been significantly associated with risk for the development of IPF. Two case reports of IPF in joiners exposed to wood dust provide context for occupational exposure to wood dust.[57] Case 1 presented at age 83 with chronic dry cough and progressive dyspnea for the preceding 6 months. Smoking history was remote, with a total of 13.5 pack-years. A diagnosis of IPF was made based on clinical findings and HRCT abnormalities consistent with UIP pattern. Occupational history revealed work in the furniture industry as a joiner from age 18-63, with exposure to wood dust while sawing, filing, and polishing wood. His specialty was mahogany wood. The work environment was dusty and technical reports indicated exposure from 3.8-5 mg/m^3.

Case 2 presented at age 73 with 3 years of progressive dyspnea and non-productive cough. He was a never-smoker. Diagnosis of IPF was made on the basis of clinical findings and HRCT pattern consistent with UIP. Occupational history revealed work for 34 years as a specialized joiner in the furniture industry in Italy and Western Germany, with exposure to wood dust occurring during the sawing and polishing of hardwood, including mahogany, oak, beech, and pine. Dust exposures were estimated at 4.8-6 mg/m^3 from 1985 to 1990 and 3.4-4.4 mg/m^3 until his retirement. He had a remote history of work for 4 years in a pulp and paper mill with exposure to dust from work with "coarse cartons."

Published case-control studies support an association between occupational exposure to wood dust and increased risk for IPF.[18,44,52] Blanc et al reported increased pooled ORs for wood dust and IPF based on 11 risk estimates in 12 published studies, with pooled OR 1.7 (95% CI 1.3-2.2).[18] Estimated pooled PAF was 4% (95% CI 2%-6%). In their case-control study of CFA, Scott et al observed a close-to threefold increase in risk for occupational exposure to wood dust that was of borderline significance: OR 2.94 (95% CI 0.87-9.90), p=0.08.[44] Occupations reported on self-administered questionnaires were classified as dirty or clean depending on the likelihood of direct exposure to airborne dust. Jobs classified as dirty for which wood dust exposure would be expected are woodworker, sawyer; craftsman; and builder, construction worker, or labourer.

In the case-control study of CFA by Hubbard et al, the job most commonly associated with wood dust exposure was woodworker, including carpenter and French polisher/cabinet maker.[52] Adjusted for

smoking status and metal dust exposure, odds of exposure to wood dust were significantly elevated whether data were collected by questionnaire alone, questionnaire with verification by telephone interview, or both: OR 1.70 (95% CI 1.01-2.92); OR 2.58 (95% CI 1.17-5.64); or 3.81 (95% CI 1.11-13.1), respectively. Increase in risk by type of wood was significant for pine only (OR 3.37 (95% CI 1.14-9.96), p=0.028, n=8), perhaps in part reflective of small numbers for each of the other wood types. PAF varied by method of data collection at 5.3%, 10.8%, and 7.1%, respectively. A positive association with duration of exposure was observed, with OR 1.12 (95% CI 1.01-1.24) per work-year exposure, p=0.02. Minimum latency was $\geq$ 5 years, with median latency of 45.5 years.

Gustafson et al observed increased risk for occupational exposure to wood dust in a case-control study of a group of IPF patients in Sweden.[46] This study was briefly described above (Organic Dust). Occupational exposure $\geq$ 5 years prior to diagnosis was required for cases to be classified as exposed. Risk for exposure to wood dust was increased for PF (OR 2.1 (95% CI 1.18-3.65), n=33). Among males with IPF, risk was significantly elevated for occupational exposure to birch (OR 2.4 (95% CI 1.18-4.92), n=13) and hardwood dust (OR 2.5, 95% CI 1.06-5.89, n=9).

Inorganic Dust: Silica, Sand/Stone

Background

Occupational exposure to silica has been associated with increased risk for airways disease, pneumoconiosis, and sarcoidosis.[58-60] Occupational exposure to silica has also been associated with increased risk for IPF, but the association is less clearly established.

Liu et al observed a significant increase in pneumoconiosis mortality at low-level silica exposure, with HR 3.00 (95% CI 1.75-5.15) at cumulative exposure 1.05-1.94 mg/m^3-years and lifetime maximum exposure concentration $\leq$ 0.35 mg/m^3.[59] At cumulative exposure >1.94 mg/m3-years, a close-to-sixfold increase in risk was observed: HR 5.88 (95% CI 3.38-10.24). The findings of Arakawa et al make it likely that some of these deaths are attributable to IPF misclassified as "pneumoconiosis."[61]

Arakawa et al investigated misclassification of IPF in silica-exposed workers in their study of 14 patients at a national hospital for occupational lung disease in Japan.[61] Of 364 patients with CT scans obtained from 1999 to 2006 as part of a silicosis surveillance program, 38 whose CT scans were interpreted as chronic interstitial pneumonia (CIP) were selected for review. Of these, 14 had initial scans that were normal or close to normal. All progressed to honeycombing over a median of 12 (range 3.7-19.1) years. Rate of progression of UIP-type abnormalities was linear overall but differed by more than tenfold among cases. For 9 (64.3%) of the 14, the last CT scan obtained during the follow-up period was interpreted as UIP; and for 5, atypical UIP. Of 8 of the 14 cases that were autopsied, all showed UIP on histopathology. Five had typical UIP and 3 atypical UIP on chest CT scan. These findings show CT patterns more consistent with IPF than silicosis in 14 silica-exposed patients, with histopathologic confirmation of UIP in 57%.

Microscopic Tissue Analysis for Inorganic Dust

Occupational exposure to silica has been associated with increased risk for IPF. Monso et al used scanning electron microscopy (SEM) and energy-dispersive X-ray analysis (EXDA) to analyze the mineral content of lung tissue obtained from 25 patients with IPF, 25 with normal lung, and 6 with pneumoconiosis.[62] UIP histology was observed in 22/25 cases diagnosed as IPF.

Silicon (Si)/sulfur (S) ratio was calculated and compared to the upper limit of normal of 0.3. Median Si/S ratio was significantly higher in IPF lung tissue compared to normal lung: 0.257 (range 0.070-2.037) vs. 0.130 (range 0.032-0.422), $p<0.007$. For pneumoconiosis, median value was 0.330 (range 0.174-0.579). Twelve (48%) IPF patients had Si/S ratio > 0.3 compared to 4 (66.7%) pneumoconiosis patients. Six of these IPF patients reported work at jobs with likely exposure to silica/silicates: quarry work; chemical industry; rubber factory; chemicals; asbestos. Three of 13 IPF patients with low Si/S ratios reported possible silica exposure: cement work, quarry, asbestos. The authors concluded that those IPF cases with an occupational history of silica exposure and Si/S ratio > 0.3 most likely had pneumoconiosis. No inorganic particles were visible on optic microscopy or polarized light microscopy (PLM).

Tsuchiya et al used PLM and SEM to examine particles and EDX spectroscopy to examine elemental deposition in the lungs of patients with IPF.[63] Si/S, aluminum (Al)/S, magnesium (Mg)/S, and iron (Fe)/S ratios were calculated. Tissue from the lungs of 15 IPF patients, 6 CTD patients, 8 CHP patients, and 6 controls was examined.

Compared to CTD patients and controls, IPF patients with and without occupational exposure had more birefringent particles ($p<0.05$). The Si/S and the Al/S ratios were significantly higher in IPF patients with no occupational exposures compared to controls ($p<0.05$) and in IPF patients with occupational exposure compared to each of the three comparison groups ($p<0.05$). Total number of particles and number of Al/S particles were higher in IPF patients compared to CTD patients. The number of silica particles was greater in IPF patients than in each of the other groups, but the difference was not significant at $p<0.05$. The authors concluded that inorganic dusts are possibly "a responsible or a modulatory factor for IPF", particularly silica and aluminum as components of aluminum silicate.

Epidemiologic Studies

For occupational exposure to silica and IPF, Blanc et al calculated a pooled OR of 1.7 (95% CI 1.2-2.4).[18] Pooled PAF was 3% (95% CI 2%-5%). For 3 of 8 epidemiologic studies of IPF for which OR for occupational exposure to silica was calculated, statistically significant or borderline significant associations were observed.[20,50,64]

In their multicentre case-control study of occupational and environmental exposures and IPF, Baumgartner et al observed a significant increase in risk for stone cutting/polishing for the group as a whole, and a borderline increase among males: OR 3.9 (95% CI 1.2-12.7), n=8 and OR 3.3 (95% CI 0.9-11.9), n=6, respectively, adjusting for age and smoking.[20] The association between IPF and silica as a stand-alone agent was not significant (OR<1.0). The association of IPF with stone cutting/polishing as a job remained significant (OR 3.2 (95% CI 1.0-10.8)) in a multivariate regression model adjusting for age and the following independent variables: smoking, hairdressing, raising birds, stone cutting/polishing, metal dust, talc, and livestock.

In the hospital-based retrospective case-control study of chronic fibrosing IIPs (IPF, NSIP) carried out by Kim et al, the proportion of never-smokers was higher among controls compared to cases overall and compared to IPF cases specifically ($p=0.000$).[47] For NSIP, observed differences in smoking status were not significant ($p=0.372$). History of environmental exposure was higher for cases overall ($p=0.044$) and for NSIP cases ($p=0.048$). More IPF cases than controls reported occupational exposure to stone/sand/silica (OR 8.84 (95% CI 1.07-73.49), n=10) and insecticides/pesticides (OR 4.45 (95% CI 1.21-

16.37), n=7). No significant associations between occupational groups or agents and NSIP were observed, perhaps due to the small number of NSIP cases.

In conditional logistic regression modelling adjusting for age, smoking, and clinical risk factors, there was a fivefold increase in risk for occupational exposure to stone/sand/silica in cases of chronic fibrosing IIP overall: OR 5.01 (95% CI 1.07-24.21), n=14. Although increase in risk was observed, associations with welding fumes/metal dust and organic dust did not achieve statistical significance. With stratification by IIP subtype, the strength of the association with stone/sand/silica increased for IPF in the adjusted model: OR 8.75 (95% CI 1.05-72.96), n=10. For NSIP, the association was not significant.

Mullen et al carried out a small case-control study of occupational and environmental exposures and DIF.[51] Inclusion criteria were lung biopsy or chest radiograph and exclusion of known causes of ILD. Information about occupational and environmental exposures and smoking was obtained from questionnaires mailed to participants by their treating physicians. Only 17 of 45 cases responded to the questionnaire. The questionnaires were reviewed by a physician trained in occupational and environmental medicine and blinded to case-control status. Individual exposures were coded according to frequency, intensity, and duration. Risk for occupational exposure to silica was significantly elevated (OR 11.00 (95% CI 1.05-115), p=0.016, n=3), but the numbers are small and the confidence intervals wide. Exposure to "any dust" did not emerge as a significant risk factor.

Paolocci et al observed a twofold increase in risk for silica exposure and IPF that was of borderline significance: OR 2.0, 95% CI 0.9-4.4. Results were presented at the European Respiratory Society Annual Congress 2013 and published in the form of an abstract.[64] In the full report published in 2018, silica was not among the self-reported exposures associated with increased risk for UIP.[21] Risk for exposure to mineral dust was borderline-elevated but mineral dust was not more specifically defined.

Inorganic Dust: Asbestos

Background

The development of pulmonary fibrosis in association with occupational exposure to asbestos exemplifies the conundrum created by the need to distinguish between IPF associated with occupational exposure to a fibrogenic agent such as silica or asbestos and pneumoconiosis. Misclassification in either direction has practical implications. Misclassification of IPF as asbestosis (or silicosis) may preclude potentially effective treatment with antifibrotics; misclassification of asbestosis as IPF may prevent appropriate workers' compensation.

Occupational history of asbestos exposure is not a foolproof guide for distinguishing IPF from asbestosis, assuming histopathology and/or HRCT pattern of UIP. Asbestosis typically occurs following 10 to 20 years of occupational exposure to asbestos but may occur after high-level exposure of months to a year or more.[8,65] A threshold cumulative dose of 25 f-years/ml has been suggested as necessary for asbestosis.[66] However, analysis of robust exposure data from cohorts of South Carolina and Chinese textile workers exposed to chrysotile asbestos by Stayner et al and Deng et al, respectively, reveals no evidence of a threshold for asbestosis.[67,68]

Calcified pleural plaques or diffuse pleural thickening on chest X-ray or HRCT may be used to verify a history of asbestos exposure and rule out a diagnosis of IPF.[8] Asbestos bodies (AB) in BAL and/or lung tissue and lung asbestos fiber burden have been suggested as markers of asbestos exposure and in the case of fiber burden, useful in quantifying prior asbestos exposure.[69] However, the reliability of

these markers is limited by the short half-life of chrysotile asbestos and the fact that chrysotile rarely forms ABs.[8,70] Chrysotile accounts for the vast majority of asbestos sold and used worldwide.

Microscopic Tissue Analysis for Asbestos Fibers

Monso et al used SEM and EXDA to search for asbestos fibers in IPF patients in whom optical microscopy failed to reveal ABs.[71] Lung tissue obtained by SLB from 24 IPF patients was examined and compared to 24 normal controls. In 2/24 (8%) IPF patients, numerous uncoated asbestos fibers were identified vs. 1 asbestos fiber in a single control. In these 2 IPF patients, the final diagnosis was asbestosis. Twenty-two of the 24 had UIP. Of these, 3 gave a history of asbestos exposure: 20 years in 1 case; 3 years in a second; and para-occupational (spouse) in a third. Of the 2 cases diagnosed as asbestosis, asbestos exposure histories were "brief occupational," and "no relevant antecedent." The authors concluded that use of standard laboratory methods likely results in overdiagnosis of IPF. However, the exposure histories of the two cases whose diagnosis was changed to asbestosis based on fiber burden do not support this conclusion.

Epidemiologic Studies

Published epidemiologic studies provide support for occupational and/or environmental exposure to asbestos as a potential contributing factor in the development of IPF.

Noting increasing mortality from asbestosis, IPF, and malignant mesothelioma (MM) in the U.K. over the time period 1968 to 2006, Barber and Fishwick examined asbestos exposure as a potential risk factor for IPF.[72] Relationships between mortality from IPF, asbestosis, and MM were tracked over the period 1968 to 2012 and compared to total annual asbestos imports into the UK during the period 1914 to 1965.[73] Annual mortality from IPF and MM among males increased steadily during the study period and tracked historic UK import of asbestos; whereas mortality from asbestosis remained stable. Mortality from IPF and MM was similar. Deaths from IPF among females increased from 1968 to 2012 and tracked historic asbestos imports. IPF mortality exceeded mortality from MM and asbestosis. A linear relationship was observed between annual mortality from IPF and MM in both males and females ($p<0.001$).

The findings of Barber et al show similar numbers of deaths from IPF and MM in males over the period 1968 to 2012 and similarity in the trajectory of increase in these deaths over the same period.[73] This time period reflects a 48-year latency and was chosen based on a previously-developed model for asbestosis. What it may say about the latency of IPF is not clear. Limitations of the study include the fact that asbestos imports do not necessarily reflect asbestos consumption, and are a crude measure of potential exposure compared to per-capita consumption.

Reynolds et al conducted a hospital-based case-control study of IPF and occupational asbestos exposure in the UK.[74] (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC988). Cases were selected from males diagnosed with IPF at one of 21 hospitals in the UK from January 2017 to January 2019; controls are age-matched males who attended an outpatient clinic during the same period. A trained interviewer used a structured questionnaire to obtain a lifetime work history and information on smoking and dyspnea from cases and controls. Occupations were coded (UK SOC) and used to create a JEM. Workplace asbestos exposures were estimated for jobs of duration $\geq$ 5 years ending prior to 1980. Blood was analyzed for the MUC5B rs3570950 genotype.

Data analysis was carried out on 494 cases and 466 controls. Sixty-six percent of cases and 63% of controls held a job with medium- or high-risk for asbestos exposure. The association between asbestos exposure as defined and IPF risk was not statistically significant, with adjusted OR 1.1 (95% CI 0.8-1.4), p=0.6. Ever-asbestos-exposed and ever-smoking were associated with a close to twofold increase (OR 1.9 (95% CI 1.3-3.6), p=0.04) in IPF risk in an interactive model. MUC5B GT or TT genotype was associated with a fivefold increase (OR 5.0 (95% CI 1.7-15), p=0.01) in IPF risk in an interactive model that included asbestos exposure and smoking. These findings support a positive interactive effect of genotype, occupational asbestos exposure, and smoking on risk for IPF.

Cumulative asbestos doses below 25 f/ml-years were not included in the data analysis. The reason is not clear. In the study by Barber et al the tracking of IPF mortality was with MM mortality and not with asbestosis mortality.[73] This finding raises the possibility that the dose-response relationship for IPF may more closely resemble that of MM, with increased risk associated with low-level asbestos exposure for short durations. Abramson et al also observed increased risk for IPF at low cumulative asbestos dose.[75]

Abramson et al conducted a case-control study of occupational and environmental exposures as risk factors for IPF in Australia.[75] Incident and prevalent cases were recruited from the Australian IPF Registry (AIPFR) established by the Australian Lung Foundation in 2012. IPF diagnosis was made using ATS/ERS/JRS/ALAT diagnostic criteria and confirmed by MDD.[26] Population-based controls matched on age, sex, and state of residence were selected using random digit dialing. Trained interviewers obtained information by telephone on demographics, family history, smoking, and occupational and environmental exposures. The Finnish Job Exposure Matrix (FinJEM) was used to code each self-reported job and assign occupational exposures. The Australian asbestos JEM (AsbJEM) was used to estimate asbestos exposures, including cumulative asbestos exposure.

Five hundred three cases and 902 controls made up the study population. The majority (> 65%) were males and ever-smokers (70% of cases, 52.7% of controls). Asbestos exposure was reported by 40% of cases and 34% of controls: OR 1.37 (95% CI 1.08-1.74), p=0.009. FH of pulmonary fibrosis was associated with increased IPF risk, with OR 12.6 (95% CI 6.52-24.4), p<0.001. No home exposures queried were associated with significant increase in IPF risk.

The FinJEM occupational exposure categories were organic dusts, inorganic mineral dusts, metal dusts, wood dusts, any metals, and other dusts (respirable dust, secondhand smoke (SHS)). Of these, SHS (OR 2.10 (95% CI 1.20-3.70)) and respirable dust (OR 1.38 (95% CI 1.04-1.82)) emerged as significantly associated with increased IPF risk in multivariate analysis adjusting for age, sex, state, and smoking. PAF was estimated at 11.6% for SHS, 7.6% for respirable dust, and 0.8% for asbestos.

Asbestos exposure as assessed using the FinJEM was not significantly associated with increase in IPF risk. However, the positive association between cumulative asbestos dose estimated using the AsbJEM developed and standardized in Australia and IPF risk was significant. Cumulative exposure was categorized in quartiles of f-years/ml as follows: $\leq$ 0.00295; 0.00296 to $\leq$ 0.00425; 0.00426 to $\leq$ 0.06255; and 0.06256 to 8.256. Compared to Q1 (referent), Q3 and Q4 were associated with significant increase in IPF risk: OR 1.46 (95% CI 1.03-2.06), p=0.034 and OR 1.61 (95% CI 1.14-2.27), p=0.007, respectively. For Q1, the significance of the association was borderline: OR 1.28 (95%CI 0.90-1.80), p=0.166. Analytical models were adjusted for age, sex, state, and smoking status and pack-years. These findings indicate a dose-response relationship for asbestos and IPF, with increase in risk at low cumulative dose.

The strengths and implications of the study by Abramson et al are enumerated in an accompanying editorial by Lee and Johannson.[76] These include the large number of cases and controls; the systematic collection of occupational histories and estimation of exposures using validated JEMs; and the examination of occupational exposure to SHS as a risk factor for IPF.

Vapours, Gases, Dusts, Fumes (VGDF)

Blanc et al identified VGDF as a risk factor for IPF.[18] The utility of this nonspecific categorization of workplace exposures in assessing occupational risk factors for respiratory disease has been demonstrated with chronic obstructive pulmonary disease (COPD).[18, 77] For purposes of assessing IPF risk, Blanc et al defined VGDF as "an inclusive category combining any of multiple exposures defined variously by each study."[18] Based upon risk estimates from 6 studies, the authors estimated pooled OR and pooled PAF for IPF at 2.0 (95% CI 1.2-3.2) and 26% (95% CI 10%-41%), respectively.[18,30,44-46,51,54]

The Ontario ODSS links data obtained from workers' compensation time-loss claims with health insurance claims data from outpatient and emergency department visits and hospitalizations. Using these data, the OCRC has examined occupational risk factors for chronic respiratory disease by industry and occupation among workers in Ontario.[22] Industries for which IPF risk for workers was highest compared to all other workers in the ODSS were gold and uranium mining: RR 3.6 and RR 3.2, respectively.[23] Occupational exposures to VGDF in these industries include metal dusts, silica, diesel exhaust, and, in uranium mining, radon progeny.

Garcia-Sancho et al observed a statistically significant association between occupational exposure to "dusts, smokes, gases or chemicals" and IPF in their case-control study of IPF in Mexico.[30] The observed OR for VGDF was 2.8 (95% CI 1.5-5.5), p=0.002, adjusting for FH, former smoking, GER history, and type II diabetes in multivariate regression analysis.

In their case-control study of prevalent cases of IPF in England and Wales, Scott et al observed associations between CFA and exposure to any dust, wood dust, asbestos, coal, stone or sand, and tobacco that were positive but not statistically significant.[44] The association between wood fires and CFA achieved statistical significance (OR 12.55 (95% CI 1.40-114.00), n=4, p=0009); although the number was small and the confidence interval wide. Mullen et al observed positive associations between DIF and environmental exposure to any dust, coal, silica wood dust, mould/mildew and any home moisture problem.[51] The association achieved statistical significance for mould/mildew (OR 16.00 (95% CI 1.62-158), p=0.003) and silica (OR 11.00 (95% CI 1.05-115), p=0.016). The small number of cases is reflected in the wide confidence intervals.

In their multicentre hospital-based study of IPF in Japan, Miyake et al observed a significant association between occupational exposure to any dust and IPF: OR 5.61 (95% CI 2.12-17.89).[54] A positive but insignificant association was observed for pesticides. In addition to certain wood dusts, Gustafson et al observed positive associations between IPF and occupational exposure to a variety of other agents: paper and textile dust, fire fumes, irritating gases (ammonia, chlorine dioxide, chlorine gas, sulphur dioxide), and rapid glues (Loctite, cyanoacrylates, Omnifit).[46] None achieved statistical significance.

In a multicentre hospital-based case-control study of 78 incident IPF cases in Japan, Koo et al observed positive associations for silica, wood dust, metal dust, and asbestos fibres.[78] Only metal dust emerged as statistically significant: OR 4.97 (95% CI 1.36-18.17). Cases were diagnosed according to 2011 ATS/ERS/JRS/ALAT criteria.[26] Two trained occupational physicians assessed occupational,

environmental, and military exposures using a structured questionnaire. Information was obtained for jobs held for ≥ 6 months; participants exposed to potentially hazardous materials for > 1 year were considered exposed.

Abramson et al observed a 38% increase in risk (OR 1.38 (95% CI 1.04-1.82), p=0.024) for IPF in association with exposure to respirable dust in a variety of workplaces, including construction, mining, manufacturing, and foundries, and at a variety of jobs, including carpentry, welding, and demolition.[75] For self-reported exposure to gases/fumes/chemicals, a 9% increase in IPF risk was observed (p=0.465).

Andersson et al examined occupational exposures and smoking as risk factors for IPF in a cohort mortality study of Swedish construction workers.[79] The cohort consisted of 389,132 construction workers who participated in at least one health examination during the period 1971 to 1993. Using data from the Swedish Death Registry for the period 1971 to 2015, the authors selected members of the cohort with IPF listed as the cause or a contributing cause of death on the death certificate. Data from the Swedish Registry of Hospital Care were used to exclude known causes of UIP and other potentially confounding diagnoses such as pneumoconiosis and HP. An information registry created from health records was used to obtain job titles, and a JEM then used to estimate workplace exposures for the following agents: asbestos; silica; wood dust; cement and concrete dust; welding fume; diesel exhaust; and vapours from epoxy, organic solvents, and isocyanates. These agents were categorized as wood dust; inorganic dust; vapours, fumes, and gases; and ultimately VGDF. Inorganic dust was defined as cement dust, concrete dust, and manmade mineral fibers (MMMF). Referents were members of the cohort without any of these exposures. Smoking status was based on the earliest health examination for which the information was available and quantified as follows: nonsmoker, ex-smoker, current moderate smoker (1-14 cigarettes/day), and current heavy smoker (≥ 15 cigarettes/day).

IPF mortality follow-up began at age 40 and continued to age 89. Silica- and asbestos-exposed workers were excluded from data analysis. Distribution by smoking status among cases exposed to VGDF was nonsmoker 42.6%, ex-smoker 15.8%, current moderate smoker 27.6%, and current heavy smoker 13.8%. Distribution was similar for cases and referents and for those exposed to fume, gases, wood dust, and inorganic dust. IPF mortality RR was not elevated overall for VGDF, adjusting for age, BMI, and smoking. Significant increase in risk attributable to VGDF and inorganic dust was elevated only among heavy smokers: VGDF RR 3.39 (95% CI 2.30-4.99) and inorganic dust RR 4.22 (95% CI 2.69-6.60). These results indicate a positive interactive effect of smoking and occupational exposure to VGDF and inorganic dusts on risk for IPF, at least among smokers of ≥ 15 cigarettes per day.

Strengths of this study are its cohort design, large numbers, availability of an internal referent group, and steps taken to minimize potential misclassification of workers exposed to asbestos and silica. Limitations include the determination of smoking status only once and at a time that could have preceded IPF diagnosis by several decades.

Kelly-Reif et al observed an association between radon exposure and IPF in their mortality study of uranium miners in Colorado.[80] The authors examined mortality from NMRD in a cohort of Colorado Plateau uranium miners followed from 1960 through 2016. The cohort consisted of 4,137 males employed for ≥ 1 month who participated in ≥ 1 medical screening between January 1, 1950, and December 31, 1960. Person-years of follow-up began January 1, 1960, or at the time of the first medical screening, and continued through December 31, 2016. Data analysis was carried out on 4,121 male underground uranium miners, of whom 88% (3,540) had died by the end of the follow-up period.

Certain members of the cohort had a history of work as hard-rock miners prior to their employment in the uranium mines.

Respiratory disease outcomes examined were asthma, COPD, IPF, pneumonia, tuberculosis, silicosis, other pneumoconiosis, and other respiratory diseases. Underlying cause of death was coded using the ICD revision in effect at the time of death. Deaths from IPF were also coded ICD-10 codes because of the possibility of misclassification with the use of earlier ICD revisions. SMRs were calculated, with expected numbers derived from standardized regional rates. Cumulative exposure to radon was calculated in working level months (WLM) and excess relative rates (ERR)/100 WLM were computed. Quantitative data on silica exposure was not available. Smoking histories were available and were taken into account in data analysis.

There were 601 deaths from NMRD. Sixty-four deaths were due to IPF coded using the ICD revision in effect at the time of death and 42 were due to IPF using the ICD-10 code. IPF SMRs were 4.77 (95% CI 3.67-6.09) and 6.22 (95% CI 4.48-8.41), respectively. IPF SMR increased with longer duration of employment and with advancing calendar period, suggesting a dose-response relationship. White and American Indian miners were at similar risk of death from IPF.

IPF was positively associated with radon exposure for the group as a whole: ERR/100 WLM 0.06 (95% CI 0.00-0.24). A stronger association was observed among those with prior history of hard-rock mining: ERR/100 WLM 0.16 (95% CI 0.02-1.06). For IPF, smoking did not affect the strength of the association with radon exposure, as it did for silicosis. The lack of air sampling data for silica is an acknowledged limitation of this study. Occupational exposure to silica or work at trades likely to be associated with exposure to silica has been associated with increased risk for IPF. Occupational exposure to silica has also been associated with increased risk for COPD.[81] In the present study radon exposure was not associated with COPD, suggesting that observed associations between radon and IPF and “other respiratory diseases” may not have been confounded by silica.

The findings of Kelly-Reif et al are consistent with those of Archer et al in 1998, the Ontario ODSS in 2019, and others.[23,82] Archer et al described chronic diffuse interstitial fibrosis (DIF) of the lung in Colorado Plateau uranium miners.[82] Lung pathology of 5 cases for whom tissue was available for review revealed DIF with honeycombing, a pattern resembling if not consistent with UIP. Anthrasilicotic nodules were observed in four. Data from the ODSS revealed risk for IPF to be highest for workers in gold and uranium mining, compared to all other workers. Potential causal associations are several and include radon.

ETIOLOGY - ENVIRONMENTAL EXPOSURES AND IPF

Smoking

The principal environmental exposure associated with IPF is smoking. Desquamative interstitial pneumonia (DIP) and RB-ILD are considered smoking-related IIPs.[5,83] The association with IPF has been more recently recognized. The mechanisms are both direct and indirect. Cigarette smoke is an irritant and causes injury to alveolar epithelial cells, initiating a series of events culminating in UIP histopathology. Smoking is also associated with telomere shortening; and telomere shortening in turn is associated with enhanced cell senescence and more rapid progression of IPF.[16] In most but not all cases of ILAs, a primary cause of telomere shortening is believed to be gene mutations. Telomere shortening is seen in both familial and sporadic cases of IPF.

Epidemiologic studies have shown both strength and consistency of the association between smoking and IPF. In their case-control study of metal or wood dust exposure and CFA risk, Hubbard et al observed a significant association between cigarette smoking and CFA (OR 1.57 (95% CI 1.01-2.43), p=0.043), with a positive dose-response relationship with pack-years that had borderline statistical significance (OR 1.05 (95% CI 0.99-1.12), p=0.117).[52]

Baumgartner et al examined the role of cigarette smoking in their case-control study of occupational and environmental risk factors for IPF.[84] Of 248 IPF cases, distribution by smoking status was 20% never smokers, 63% former smokers, and 17% current smokers. Proportions were similar for smokers with $\leq$ 20, 21-40, and > 40 pack-years. Ever smoking, former smoking and smoking 21-40 pack-years were associated with progressive increase in risk for IPF: OR 1.59 (95% CI 1.1-2.4), OR 1.90 (95% CI 1.3-2.9), and OR 2.26 (95% CI 1.3-3.8), respectively. No significant associations were observed for pipe, cigar, or marijuana smoking, or for domestic exposure to SHS. Those smokers who reported a history of an occupational exposure (> 10 hours/week) had a fourfold increase in IPF risk (OR 4.10 (95% CI 1.3-13.3); among smokers who reported no occupational exposure, increase in risk was lower but nevertheless significant (OR 1.75 (95% CI 1.0-3.10)).

In a subsequent publication with focus on occupational and environmental exposures as IPF risk factors, Baumgartner et al observed a smoking-related increase in risk (OR 1.8 (95% CI 1.2-2.7), adjusting for age and other exposure variables in a multivariate model.[20] There was evidence of synergism between smoking and livestock exposure on risk for IPF: OR 0.8 (95% CI 0.2-3.1) for livestock exposure alone; OR 1.7 (95% CI 1.1-2.5) for smoking alone; and OR 6.1 (95% C 2.1-17.6) for exposure to both livestock and smoking. For none of the other occupational exposures was there evidence of a significant interactive effect with smoking.

Ekstrom et al examined associations of smoking with PF and IPF in their case-control study.[45] A dose-response relationship was observed for pack-years and both PF and IPF. For IPF, smoking $\geq$ 20 pack-years was associated with a greater than twofold increase in risk compared to smoking 1-9 pack years (OR 2.5 (95% CI 1.3-5.0)) and 10-19 pack-years (OR 2.10 (95% CI 1.20-3.68)). In males, an interactive effect of smoking and occupational exposure was observed for PF and IPF. For IPF, ever smoking > 10 years prior to diagnosis in the absence of an occupational exposure was associated with a 44% increase in risk that was not statistically significant. Smoking and occupational exposure together were associated with a threefold increase in IPF risk: OR 2.96 (95% CI 1.34-6.52).

In the cohort mortality study by Andersson et al, a dose-response relationship was observed for smoking and IPF for referents not occupationally-exposed and for subjects exposed to VGDF and inorganic dusts.[79] For nonexposed referents who smoked, IPF risk was higher and similar among current moderate and heavy smokers compared to ex-smokers, with RR 2.55 (95% CI 1.78-3.65) observed among current heavy smokers. For IPF cases, risk among ex-smokers and current moderate smokers exposed to VGDF and inorganic dusts was similar to that of nonexposed referents. Among current heavy smokers with these occupational exposures, IPF risk was increased more than threefold for VGDF and over fourfold for inorganic dust consistent with a positive interactive effect in this group.

The case-control study by Abramson et al is one of the few to examine occupational exposure to SHS as a risk factor for IPF.[75] Self-reported exposure to SHS at work was not associated with increased IPF risk, although it was the most-commonly reported exposure at >70% for cases and controls. However, when the FinJEM was used to estimate occupational exposures a twofold increase in IPF risk

was observed (OR 2.10 (95% CI 1.20-3.70), p=0.010) for SHS, adjusting for age, sex, state, and smoking status. Forty-nine percent of cases and 29% of controls had SHS exposure at work.

In a recently-published systematic literature review and meta-analysis of the role of occupational and environmental risk factors for IPF, Pauchet et al adjusted for smoking for general dust, and organic, metal, and wood dust.[85] IPF risk for general dust, metal dust, and organic dust remained significantly elevated after taking smoking into account. For general dust and IPF, overall OR was 1.32 (95% CI 1.08-1.63); and smoking-adjusted OR was 1.45 (95% CI 1.04-2.03). For organic dust, ORs were 1.72 (95% CI 1.20-2.46), and 2.50 (95% CI 1.49-4.22), respectively. For metal dust, ORs were 1.42 (95% CI 1.05-1.92), and 1.87 (95% CI 1.16-3.0), respectively. For wood dust, the relationship between occupational exposure and IPF was no longer significant after adjusting for smoking: overall OR 1.32 (95% CI 1.02-1.71); smoking- adjusted OR 1.16 (95% CI 0.86-1.61).

Agent Orange

In their study of the epidemiology of IPF among U.S. Veterans, Kaul et al observed an increase in prevalence of the disease during the study period 2010-2019, from 276 cases/100,000 in 2010 to 725 cases/100,000 in 2019.[86] Agent Orange exposure was investigated as a possible etiologic factor. Agent Orange is a chemical herbicide and defoliant used during the Vietnam War to defoliate the jungles in Vietnam, and in other locations as an herbicide in the same timeframe. It is composed of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid.[86] The latter was contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin).

Kaul et al conducted a cohort study of U.S. Veterans who served in Vietnam and were at risk for exposure to Agent Orange.[87] Exposure was presumed on the basis of an "Agent Orange Flag" on a Veteran's military discharge papers. An Agent Orange Flag was placed on the file of Veterans who had received a Vietnam Campaign Medal which indicated "boots on the ground" service in Vietnam and risk for exposure to Agent Orange. For a determination of IPF, Veterans Health Administration (VHA) electronic medical records data were accessed. Cases were those with an ICD-9 or ICD-10 code for IPF and no other diagnostic code for ILD. IPF cases with presumed exposure were compared to those without presumption of exposure. Co-variates included in the regression models were age, race, ethnicity, smoking, rural vs. urban residence, and branch of military service. In separate analyses, the authors used only ICD codes with greatest IPF specificity and restricted branch of service to the army. The army was considered the branch most highly exposed to Agent Orange.

Results showed that 26% (n=948,103) of the 3.6 million male Vietnam Veterans who accessed health care through the VA during the time 2010 through 2019 were exposed to Agent Orange. Those exposed were more likely to be White, live in rural areas, and have served in the army (vs. other branches of the Armed Services). A statistically significant increase in risk for IPF was observed among exposed vs. unexposed Veterans: unadjusted model – OR 1.14 (95% CI 1.12-1.16), p<0.001; adjusted model – OR 1.08 (95% CI 1.06-1.10), p<0.001. Neither restriction of service to the army nor restriction of ICD codes notably altered outcome in the adjusted models: OR 1.13 (95% CI 1.13-1.18) and OR 1.11 (95% CI 1.05-1.17), respectively. Inclusion of both independent variables in the same adjusted model resulted in a 17% (95% CI 1.09-1.25) increase in IPF risk associated with Agent Orange exposure v. 8% in the unrestricted model.

A limitation of the Kaul study is the use of ICD codes to define IPF. This limitation is mitigated but not eliminated by the fact that the same method of defining IPF was applied to both exposed and

unexposed groups. Agent Orange exposure was broadly defined, as more specific measures of exposure were not available. Nevertheless, IPF risk was higher when military service was restricted to the most highly-exposed branch: 13% vs. 8%. These findings are consistent with previously-published reports of associations between IPF and work at jobs where exposure to pesticides/insecticides/herbicides would not be unusual.[18,20-21]

PROGNOSIS

Prognosis is poor for IPF patients.[14] For those 65 years of age or older, a median survival of 3.8 (95% CI 3.5-3.8) years was observed by Raghu et al in their study of a 5% randomly-selected sample of Medicare beneficiaries in the U.S.[88] Male gender and older age were associated with shorter survival, findings consistent with those of Sgalla et al.[89] Khor et al conducted a systematic review of prognosis in IPF patients who had not received antifibrotic therapy.[90] Analytical variables included type of study (randomized controlled trial (RCT) vs. cohort) and criteria used to diagnose IPF.[4,26] Pooled mean overall survival was 4 (95% CI 3.7-4.6) years for studies with follow-up of 10 years.

Occupational and environmental exposures have not been well-studied with regard to their effect on prognosis in patients with IPF. Barber et al examined IPF mortality and its relationship to asbestos importation in the UK but survival following IPF diagnosis was not an outcome of interest.[72]

De Sadeleer et al examined and compared survival in IPF patients without exposure to birds or mould (Group A), IPF patients with exposure to birds/mould (Group B), and CHP patients (Group C).[50] Median survival was longest in CHP patients and shortest in IPF patients without bird/mould exposure. Antifibrotic therapy resulted in better outcome in both IPF groups, but the effect was greater in Group B: HR 0.44 Group A and HR 0.12 Group B, p=0.20. These results suggest that occupational and/or environmental exposure to birds/mould is associated with improved survival in IPF patients compared to no such exposure.

The Korean Interstitial Lung Disease Research Group conducted a national survey of incident IPF cases to examine the relationship of clinical characteristics and survival to occupation.[91] The multicentre survey enrolled 1,311 IPF patients during the period January 1, 2003 to December 31, 2007. Diagnosis was made using 2002 ATS/ERS criteria.[4] Information on occupation was coded using the International and Korean Standards of Occupation Classification. Exposures were categorized into 5 groups: unemployed or homemaker (n=628); farmer, fisher, rancher (n=230); sales or service (n=131); clerical or professional (n=151); and dust-exposed (n=171). Dusts of interest were wood, metal, sand, stone, diesel, and chemical.

Significant differences in outcome were observed among the occupational groups for age ($p<0.001$); proportion of males ($p<0.001$); smoking status ($p<0.001$) but not pack-years; and duration of symptoms at diagnosis ($p=0.004$). Those in the dust-exposed group were younger (average age 61.3 $\pm$ 8.6 years); had the highest percentage of males (93.6%) and current smokers (38.0%); and had longer duration of symptoms at diagnosis (17.0 $\pm$ 28.2 mos.). Prevalence of comorbidities did not differ by occupational group ($p>0.242$).

IPF mortality risk was highest in the dust-exposed group compared to the other occupational groups, with HR 1.813 (95% CI 1.049-3.133), p=0.033. The wood- or chemical-dust subgroup experienced the worst prognosis. The best prognosis was observed in those with occupational exposure to diesel particulate and metal dust; exposure to sand or stone dust was associated with intermediate prognosis.

These findings show that IPF patients with occupational exposure to dust have onset of disease at a younger age, longer duration of symptoms prior to diagnosis, and worse prognosis compared to other occupational groups. That the group with the highest mortality HR is the youngest is inconsistent with the findings of others that older age predicts shorter survival.[88,89] The apparent contradiction between younger age at diagnosis and longer duration of symptoms may reflect a lower level of suspicion on the part of the clinician for a diagnosis of IPF because of the patient's younger-than-expected age.

Lee et al conducted a study of consecutive patients seen from May to October 2018 at a tertiary ILD clinic in the U.S.[92] One hundred fifty-four patients were enrolled in the study. The most common ILD subtypes were CTD-ILD, IPF, and HP: CT-ILD 42%, n=66; IPF 26%, n=41; and HP 14%, n=22. Diagnosis was made at MDD. Information was obtained about inhalational exposures at work and at home, including with hobbies. Occupational exposure was defined as workplace exposure to an agent previously associated with ILD. Exposures were categorized as any, occupational, domestic, and multiple. The most common occupational exposures among males were metal dust and silica; among females, organic material.

Twenty-five deaths and 10 lung transplants occurred between enrollment and the end of follow-up on September 30, 2020. Transplant-free survival was worse in the group with any inhalational exposure compared to the group with no inhalational exposure, adjusting for age and gender: HR 2.58 (95% CI 1.13-5.92), p=0.025. Mean survival was 25.6 months in the exposed group and 26.9 months in the unexposed group. Further adjusting for the GAP score (based on gender, age, and pulmonary function) and smoking (pack-years), the difference in survival was not statistically significant: HR 1.82 (95% CI 0.77-4.27), p=0.17.

Limitations of the present study with regard to prognosis are short follow-up time (24-29 months) and lack of information on prior treatment. Because survival was not analyzed by ILD subtype, it is not possible to examine the effect of inhalational exposures on IPF prognosis.

TREATMENT

There is no known cure for IPF. Treatment modalities include supplemental oxygen, pulmonary rehabilitation, lung transplantation, and antifibrotic drugs. Three- and 5-year survival following lung transplant is 66% and 53%, respectively.[93]

Antifibrotic therapy has been shown to be safe and effective in slowing progression of IPF.[93] In 2014 the U.S. Food and Drug Administration (FDA) approved the use of the antifibrotic drugs nintedanib and pirfenidone in IPF; these drugs were approved by Health Canada in 2015 and 2012, respectively. . In RCT each was shown to reduce decline in forced vital capacity (FVC) by 50% over the course of 1 year and to have some effectiveness in reducing the frequency of acute exacerbations and hospitalizations. In a study by Dempsey et al using U.S. health insurance claims data, treatment with these drugs resulted in improved 2-year survival in 1,255 treated patients vs. the same number of untreated patients (HR 0.77 (95% CI 0.62-0.98), p=0.034).[94] Risk of acute hospitalization also declined in the treated group (HR 0.70 (95% CI 0.61-0.80), p<0.001). No difference in efficacy between the 2 drugs was observed.

Nintedanib and pirfenidone slow but do not halt progression of IPF. Each has side effects that render the drug intolerable for some patients. The survival benefit is limited for these drugs as solo therapy, but the effect of using these drugs in combination is unknown. Novel therapies are currently being investigated.[95] These include the recombinant human monoclonal antibody pamrevlumab, which

binds to and inhibits connective tissue growth factor (CTGF). CTGF is a protein that plays a role in biologic activities that include tissue repair and fibrosis.

ASSESSMENT

IPF is the most common of the IIPs. Incidence appears to be increasing, particularly among older males. Our understanding of pathogenesis continues to evolve and drive new and novel therapies. Diagnostic guidelines have been established by respected international pulmonary societies and then revised as we learn more about the disease.

The "inflammatory theory" of IPF was discarded in the 1990s, and the pathologic classification of IIPs revised after studies using electron microscopy showed alveolar epithelial cell injury and foci of subepithelial cell fibrosis in IPF.[24, 96] Overlapping paradigms of IPF pathogenesis are 1) alveolar epithelial cell injury and 2) injury to epithelial and endothelial cell BMs at the alveolar-capillary junction, with 3) impairment in repair mechanisms in both cases.[2,25] Remodeling of lung tissue and replacement of normal architecture with fibrosis is the result.

Epithelial cell injury results from inhalation and persistence in lung tissue of toxic irritants and antigenic material. In 1996 Churg described pathophysiologic mechanisms and consequences of uptake of inhaled mineral particles by tracheobronchial and alveolar epithelial cells, noting that such uptake is an important mechanism of cell injury.[97] Among the types of mineral particles observed in lung epithelial cells at autopsy are silica, asbestos, talc, and titanium dioxide. Predisposing the lung to injurious effects of these toxicants are male gender, older age, family history, specific genetic mutations such as MUC5B rs35705950, and short telomeres. Telomeres shorten normally with age. Genetic factors hasten this process, as does cigarette smoke. To the extent that cigarette smoke is associated with increased risk for telomere shortening in vulnerable populations, it follows logically that the same would be true for inhalational occupational exposures. As Moore et al point out, "… a number of genetic and nongenetic risk factors may independently (and additively) contribute to the risk and pathogenic heterogeneity of IPF."[34]

Epidemiologic studies have shown positive associations between occupational exposure to certain irritant and antigenic particles and IPF risk. These associations have been consistent over time and across different studies. Despite the number and consistency of these epidemiologic studies, information about two important variables is limited: dose-response relationship and latency. For example, Reynolds et al examined cumulative asbestos dose and IPF risk.[74] Data analysis was limited to asbestos dose $\geq$ 25 f/mL-years, considered by some to be a threshold for asbestosis. However, Barber et al observed an increase in IPF mortality that tracked with malignant mesothelioma mortality, not with mortality from asbestosis.[73] Abramson et al observed increased IPF risk at low cumulative asbestos dose.[75]

Few studies have examined the effect of occupational exposures on the clinical course of patients with IPF. Lee et al observed longer duration of symptoms, younger age at diagnosis, and more rapid progression to death in IPF patients who worked in a dust-exposed job vs. other occupational groups.[91] De Sadeleer et al observed improved survival in IPF patients with occupational exposure to birds/mould vs. IPF patients without such exposures.[50]

The significance of the findings of Lee et al and De Sadeleer et al is not clear; but Culver et al offer a pathway to better understanding, monitoring, and treatment of the clinical manifestations of IPF, namely the establishment and proper maintenance of IPF patient registries.[91,50,98] Nett et al have

proposed in addition the use of IPF patient registries to obtain occupational and environmental exposure information in a standardized fashion that would allow pooling of data for epidemiologic analyses.[99] Detailed occupational history that allows not only determination of nature and type of exposure but also estimation of dose and dose-response relationships is a necessary step as it is key to primary prevention. These analyses would improve our understanding of associations between specific occupational exposures and IPF risk. Culver and Kim acknowledge that expanding the scope of IPF patient registries in this way would "help clinicians and policy-makers identify which particle types are likely to injure the epithelium the most, driving the progression of fibrosis."[100]

As our understanding of the pathogenesis and etiology of IPF has grown, so too have questions about nomenclature. Is "idiopathic pulmonary fibrosis" an appropriate name for this condition? Wolters et al have proposed renaming IPF.[3] The use of a committee of "stakeholders" is suggested to consider the following: Is IPF idiopathic? Do definable subgroups exist? Does the term fibrosis mischaracterize a disease whose pathogenesis involves primarily injured lung epithelial cells? These are reasonable questions. On the other hand, Wells et al propose maintaining the status quo, at least for now, arguing: "The IIPs are not all idiopathic, not always interstitial and seldom pneumonias, but the term has been retained because there is a widespread understanding of, and clinical utility to, its meaning with the vast majority of publications since 2002 based on the 2002 IIP criteria."[4,101]

These discussions about the renaming of IPF fail to consider another variable: workers' compensation. A diagnosis of "idiopathic" pulmonary fibrosis provides an escape hatch that allows denial of a worker's compensation claim based on the name alone. As is the case with IIPs as a group, not all cases of IPF are idiopathic.

CONCLUSIONS

Epidemiologic evidence supports a causal association between inhalational occupational and environmental exposures and increased risk for IPF. Associations are strongest and most consistent for organic dust, metal dust, wood dust, and inorganic dust. Smoking is a risk factor for IPF and may interact with certain of these occupational exposures in a way that affects risk.

Smoking has been associated with injury to alveolar epithelial cells. It is illogical to think that inhalation of occupational and environmental particulate matter, gases, and vapours would not have a similar effect. The uptake of mineral particles by airway and alveolar epithelial cells with cytotoxic effects has been demonstrated.

Collection of detailed occupational and environmental histories in a standardized fashion should be added to the responsibilities of IPF patient registries. The importance of such information and how to get it should be emphasized in the clinical setting.

There are nonoccupational risk factors for IPF. These include older age, male gender, family history, gene mutations, short telomere syndrome, smoking, and GER with microaspiration. The presence of one or more of these risk factors does not preclude occupational exposures as substantial contributing factors in risk for disease. In fact, as we see with smoking, such risk factors may increase susceptibility to occupational exposures.

Finally, "idiopathic" in "idiopathic pulmonary fibrosis" should not deter just compensation for patients whose IPF is work-related. Instead, the name must be considered in the context of all that we know about the multifactorial nature of IPF, at least until we know enough to pick the right name.

REFERENCES

1. Tighe RM, Meltzer EB, Noble PW. Idiopathic pulmonary fibrosis. In: Grippi MA, ed-in-chief. *Fishman's Pulmonary Diseases and Disorders*. Fifth Edition. Toronto: McGraw Hill Education. 2015, pp. 842-858.
2. Ley B, Collard HR, King TE, Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. Concise Clinical Review. *Am J Respir Crit Care Med*. 2011;183:431-440.
3. Wolters PJ, Blackwell TS, Eickelberg O, Loyd JE, Kaminski N, Jenkins G, et al. Time for a change: is idiopathic pulmonary fibrosis still idiopathic and only fibrotic? *Lancet Respir Med*. 2018;6(2):154-160.
4. Travis WD, King TE, Jr., Co-Chairs, Core Panel. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med*. 2002;165:277-304.
5. Travis WD, Costabel U, Hansell DM, King TE, Jr., Lynch DA, Nicholson AG, et al. An official American Thoracic Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med*. 2013;188(6):733-748.
6. Montesi SB, Fisher JH, Martinez FJ, Selman M, Pardo A, Johannson KA. Update in interstitial lung disease 2019. Pulmonary, sleep, and critical medicine. *Am J Respir Crit Care Med*. 2020;202(4):500-507.
7. Trethewey SP, Walters GI. The role of occupational and environmental exposures in the pathogenesis of idiopathic pulmonary fibrosis: a narrative literature review. *Medicina*. December 10, 2018. https://doi.org/10.3390/medicina54060108.
8. Walters GI. Occupational exposures and idiopathic pulmonary fibrosis. *Curr Opin Allergy Clin Immunol*. 2020;20:103-111.
9. King TE, Jr., Chair. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. *Am J Respir Crit Care Med*. 2000;161:646-664.
10. Hutchinson J, Fogarty A, Hubbard R, McKeever T. Global incidence and mortality of idiopathic pulmonary fibrosis: a systematic review. *Eur Respir J*. 2015;46:795-806.
11. Hopkins RB, Burke N, Fell C, Dion G, Kolb M. Epidemiology and survival of idiopathic pulmonary fibrosis from national data in Canada. *Eur Respir J*. 2016;48:187-195.
12. Cox IA, Otahal P, de Graaff B, Corte TJ, Moodley Y, Zappala C, et al. Incidence, prevalence and mortality of idiopathic pulmonary fibrosis in Australia. *Respirology*. 2021;1-8. DOI: 10.1111/resp.14194.
13. Maher TM, Bendstrup E, Dron L, Langley J, Smith G, Khalid JM, et al. Global incidence and prevalence of idiopathic pulmonary fibrosis. *Respiratory Research*. 2021;22:197. https://doi.org/10.1186/s12931-021-01791-z.
14. Strongman H, Kausar I, Maher TM. Incidence, prevalence, and survival of patients with idiopathic pulmonary fibrosis in the UK. *Adv Ther*. 2018;35:724-736.
15. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, et al. Diagnosis of idiopathic pulmonary fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med*. 2018;198(5): e44-e68.
16. Courtwright AM, El-Chermaly S. Telomeres in interstitial lung disease: the short and the long of it. Focused review. *Ann Am Thorac Soc*. 2019;16(2):175-181.
17. Stock CJW, Renzoni EA. Telomeres in interstitial lung disease. *Review. J Clin Med*. 2012;10, 1384. https://doi.org/10.3390/jcm10071384.

18. Blanc PD, Annesi-Maesano I, Balmes JR, Cummings KJ, Fishwick D, Miedinger D, et al. The occupational burden of nonmalignant respiratory diseases. An official American Thoracic Society and European Respiratory Society statement. *Am J Respir Crit Care Med*. 2019;199(11):1312-1334.
19. Reynolds C, Feary J, Culinan P. Occupational contributions to interstitial lung disease. *Clin Chest Med*. 2020;41:697-707.
20. Baumgartner KB, Samet JM, Coultas DB, Stidley CA, Hunt WC, Colby TV, et al. Occupational and environmental risk factors for idiopathic pulmonary fibrosis: a multicenter case-control study. *Am J Epidemiol*. 2000;152:307-315.
21. Paolocci G, Folletti I, Toren K, Ekstrom M, Dell'Orno M, Muzi G, et al. Occupational risk factors for idiopathic pulmonary fibrosis in Southern Europe: a case-control study. *BMC Pulmonary Medicine*. 2018;18:75. https://doi.org/10.1186/s12890-018-0422-2.
22. Occupational Cancer Research Centre, Ontario Health. Chronic respiratory report: highlights from the occupational disease surveillance system. Toronto, ON: 2022.
23. The Occupational Disease Surveillance System. Occupational Cancer Research Centre. Idiopathic Pulmonary Fibrosis. Toronto ON. 2019. htpps://www.odsp-ocrc.ca/ipf/.
24. Nicholson AG, Rice AJ. Interstitial lung diseases. In: Hasleton P, Flieder DB, eds. *Spencer's Pathology of the Lung*. Sixth Edition. Cambridge: University Printing House. 2013, pp. 366-408.
25. Strieter RM, Mehrad B. New mechanisms of pulmonary fibrosis. *Chest*. 2009;136:1364-1370.
26. Raghu G, Collard HR, Egan JJ, Martinez FJ, Behr J, Brown KK, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med*. 2011;183:788-824.
27. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, et al. Idiopathic pulmonary fibrosis (an update) and progressive pulmonary fibrosis in adults. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med*. 2022;205(9):e18-e47.
28. Flaherty KR, King TE, Jr., Raghu G, Lynch JP III, Colby TV, Travis WD, et al. Idiopathic pulmonary pneumonia. What is the effect of a multidisciplinary approach to diagnosis? *Am J Respir Crit Care Med*. 2004; 170:904-910.
29. Ageely G, Souza C, De Boer K, Zahra S, Gomes M, Voduc N. The impact of multidisciplinary discussion (MDD) in the diagnosis and management of fibrotic interstitial lung diseases. *Canadian Respiratory Journal*. 2020. https://doi.org10.1155/2020/9026171.
30. Garcia-Sancho C, Buendia-Roldan I, Fernandez-Plata MR, Navarro C, Perez-Padilla R, Vargas MH, et al. Familial pulmonary fibrosis is the strongest risk factor for idiopathic pulmonary fibrosis. *Respiratory Medicine*. 2011;105:1902-1907.
31. Steele MP, Speer MC, Loyd JE, Brown K, Herron A, Slifer SH, et al. Clinical and pathologic features of familial interstitial pneumonia. *Am J Respir Crit Care Med*. 2005;172:1146-1152.
32. Hodgson U, Laitinen T, Tukiainen P. Nationwide prevalence of sporadic and familial idiopathic pulmonary fibrosis: evidence of founder effect among multiplex families in Finland. *Thorax*. 2002;57:338-342.
33. Sgalla G, Lovene B, Calvello M, Ori M, Varone F, Richeldi L. Idiopathic pulmonary fibrosis: pathogenesis and management. *Respiratory Research*. 2018;19:32. https://doi.org/10.1186/s12931-018-0730-2.
34. Moore C, Blumhagen RZ, Yang IV, Walts A, Powers J, Walker T, et al. Resequencing study confirms that host defense and cell senescence gene variants contribute to the risk of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2019;200(2):199-208.

35. Hobbs BD, Putman RK, Araki T, Nishino M, Gudmundsson G, Gudnason V, et al. Overlap of genetic risk between interstitial lung abnormalities and idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2019;200(11):1402-1413.
36. Peljto A, Zhang Y, Fingerlin TE, Ma S-F, Garcia JGN, Richards TJ, et al. Association between the MUC5B promoter polymorphism and survival in patients with idiopathic pulmonary fibrosis. JAMA. 2013;309(21):2232-2239.
37. Allen RJ, Porte J, Braybrooke R, Flores C, Fingerlin TE, Oldham JM, et al. Genetic variants associated with susceptibility to idiopathic pulmonary fibrosis in people of European ancestry: a genome-wide association study. *The Lancet*. 2017;5:869-880.
38. Armanios MY, Chen J J-L, Cogan JD, Alder JK, Ingersoll RG, Markin C, et al. Telomerase mutations in families with idiopathic pulmonary fibrosis. *N Engl Med*. 2007;356(13):1317-1326.
39. Newton CA, Batra K, Torrealba J, Kozlitina J, Glazer CS, Aravena C, et al. Telomere-related lung fibrosis is diagnostically heterogeneous but uniformly progressive. *Eur Respir J*. 2016;48:1556-1558.
40. Raghu G, Meyer KC. Silent gastro-oesophageal reflux and microaspiration in IPF: mounting evidence for anti-reflux therapy? *Eur Respir J*. 2012;39:242-245.
41. Tobin RW, Pope CE II, Pellegrini CA, Emond MJ, Sillery J, Raghu G. Increased prevalence of gastroesophageal reflux in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 1998;158:1804-1808.
42. Lee JS, Song JW, Wolters PJ, Elicker BM, King TE, Jr, Kim DS, et al. Bronchoalveolar lavage pepsin in acute exacerbation of idiopathic pulmonary fibrosis. Eur Respir J. 2012;39:352-358.
43. Morell F, Villar A, Montero M-A, Munoz X, Colby TV, Pipvath S, et al. Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-control Study. *Lancet Respir Med*. 2013;1:685-694.
44. Scott J, Johnston I, Britton J. What causes cryptogenic fibrosing alveolitis? A case-control study of environmental exposure to dust. *Br Med J*. 1990;301:1015-1017.
45. Ekstrom M, Gustafson T, Boman K, Nilsson K, Tomling G, Murgia N, et al. Effects of smoking, gender and occupational exposure on the risk of severe pulmonary fibrosis: a population-based case-control study. *BMJ Open*. 2014;4:e004018. Doi:10.1136/bmjopen-2013-004018.
46. Gustafson T, Dahlman-Hoglund A, Nilsson K, Strom K, Tornling G, Toren K. Occupational exposure and severe pulmonary fibrosis. *Respiratory Medicine*. 2007;101:2207-2212.
47. Kim SY, Kang DM, Lee HK, Kim KH, Choi J. Occupational and environmental risk factors for chronic fibrosing idiopathic interstitial pneumonia in South Korea. *JOEM*. 2017;59(11):e221-e226.
48. Salisbury ML, Myers JL, Belloli EA, Kazerooni EA, Martinez FJ, Flaherty KR. Diagnosis and treatment of fibrotic hypersensitivity pneumonia. Pulmonary Perspective. *Am J Respir Crit Care Med*. 2017;196(6):690-699.
49. Raghu G, Remy-Jardin M, Ryerson CJ, Myers JL, Kreuter M, Vasakova M, et al. Diagnosis of hypersensitivity pneumonitis in adults. An official ATS/ERS/JRS/ALAT clinical practice guideline. *Am J Respir Crit Care Med*. 2020;202(3): e36-e69.
50. De Sadeleer LJ, Verleden SE, De Dycker E, Yserbyt J, Verschakelen JA, Verbeken EK, et al. Clinical behaviour of patients exposed to organic dust and diagnosed with idiopathic pulmonary fibrosis. *Respirology*. 2018;23:1160-1165.
51. Mullen J, Hodgson MJ, DeGraff AC, Thomas G. Case-control study of idiopathic pulmonary fibrosis and environmental exposures. *J Occup Environ Med*. 1998;40(4):363-367.

52. Hubbard R, Lewis S, Richards K, Johnston I, Britton J. Occupational exposure to metal or wood dust and aetiology cryptogenic fibrosing alveolitis. *The Lancet*. 1996;347:284-289.
53. Hubbard R, Cooper M, Antoniak M, Venn A, Khan S, Johnston I, et al. Risk of cryptogenic fibrosing alveolitis in metal workers. *Lancet*. 2000;355:466-467.
54. Miyake Y, Sasaki S, Yokoyama T, Chida K, Azuma A, Suda T, et al. Occupational and environmental factors and idiopathic pulmonary fibrosis in Japan. *Ann Occup Hyg*. 2005;49(3):259-265.
55. Pinheiro GA, Antao VC, Wood JM, Wassell JT. Occupational risks for idiopathic pulmonary fibrosis mortality in the United States. *Int J Occup Environ Health*. 2008;14(2):117-123.
56. Iwai K, Mori T, Yamada N, Yamaguchi M, Hosoda Y. Idiopathic pulmonary fibrosis. Epidemiologic approaches to occupational exposures. *Am J Respir Crit Care Med*. 1994;150:670-675.
57. Ricco M. Lung fibrosis and exposure to wood dusts: two case reports and review of the literature. *Medycyna Pracy*. 2015;66(5):739-747.
58. Hnizdo E, Vallyathan V. Chronic obstructive pulmonary disease due to occupational exposure to silica dust: a review of epidemiological and pathological evidence. *Occup Environ Med*. 2003;60:237-243.
59. Liu Y, Zhou Y, Hnizdo E, Shi T, Steenland K, Xinjian H, et al. Total and cause-specific mortality risk associated with low-level exposure to crystalline silica: a 44-year cohort study from China. *Am J Epidemiol*. 2017;186(4):481-490.
60. Oliver LC, Zarnke AM. Sarcoidosis. An occupational disease? *Chest*. 2021;160(4):1360-1367.
61. Arakawa H, Fujimoto K, Honma K, Suganuma N, Morikubo H, Saito Y, et al. Progression from near-normal to end-stage lungs in chronic interstitial pneumonia related to silica exposure: long-term CT observations. *AJR*. 2008;191:1040-1045.
62. Monso E, Tura JM, Marsal M, Morell F, Pujadas J, Morera J. Mineralogical microanalysis of idiopathic pulmonary fibrosis. *Arch Environ Health*. 1990;45(3):185-188.
63. Tsuchiya K, Inase N, Ichinose S, Usui Y, Miyazaki Y, Ohtani Y, et al. Elemental analysis of inorganic dusts in lung tissues of interstitial pneumonias. *J Med Dent Sci*. 2007;54:
64. Paolocci G, Nicolic V, Folletti I, Kjell T, Gambelunghe A, dell'Omo M, et al. Risk factors for idiopathic pulmonary fibrosis in Southern Europe: a case-control study. European Respiratory Society Annual Congress 2013. Abstract No. 4172. Publication No. P1912.
65. Guidotti TL, Chair. Diagnosis and initial management of nonmalignant diseases related to asbestos. *Am J Respir Crit Care Med*. 2004;170:691-715.
66. Browne K. A threshold for asbestos related lung cancer. *Brit J Ind Med*. 1986;43:556-558.
67. Stayner L, Smith R, Bailer J, Gilbert S, Steenland K, Dement J, et al. Exposure-response analysis of risk of respiratory disease associated with occupational exposure to chrysotile asbestos. *Occup Environ Med*. 1997;54:646-652.
68. Deng Q, Wang X, Wang M, Lan Y. Exposure-response relationship between chrysotile exposure and mortality from lung cancer and asbestosis. *Occup Environ Med*. 2012;69:81-86.
69. Wolff H, Vehmas T, Oksa P, Rantanen J, Vaino H, reporters. Asbestos, asbestosis, and cancer, the Helsinki criteria for diagnosis and attribution 2014: recommendations. Consensus report. *Scand J Work Environ Health*. 2015;41(1):5-15.
70. Collegium Ramazzini Position Statement. Comments on the 2014 Helsinki Consensus Report on Asbestos. 2015.
71. Monso E, Tura JM, Pujadas J, Morell F, Morera J. Lung dust content in idiopathic pulmonary fibrosis: a study with scanning electron microscopy and energy dispersive x ray analysis. *Brit J Ind Med*. 1991;48:327-331.

72. Barber CM, Fishwick D. Importance of past occupational exposures in the rising incidence of idiopathic pulmonary fibrosis in the UK. PostScript. Thorax. 2012;67(3):264.
73. Barber CM, Wiggans RE, Young C, Fishwick D. UK asbestos imports and mortality due to idiopathic pulmonary fibrosis. *Occupational Medicine*. 2016;66:106-111.
74. Reynolds CJ, Sisodia R, Barber C, Minelli C, De Matteis S, Mofatt M, et al. What role for asbestos in idiopathic pulmonary fibrosis? Findings from the IPF job exposures study. *Occup Environ Med*. 2023;80(2):97-103
75. Abramson MJ, Murambadoro T, Alif SM, Benke GP, Dharmage SC, Glaspole I, et al. Occupational and environmental risk factors for idiopathic pulmonary fibrosis in Australia: case-control study. *Thorax*. 2020;75(10):864-869.
76. Lee CT, Johannson KA. Occupational exposures and IPF: when the dust unsettles. Editorial. *Thorax*. 2020;75(10):828-829.
77. Balmes J, Becklake M, Blanc P, Henneberger P, Kreiss K, Mapp C, et al. Occupational contribution to the burden of airway disease. American Thoracic Statement. Am J Respir Crit Care Med. 2003;167:787-797.
78. Koo JW, Myong J-P, Yoon H-K, Rhee CK, Kim JS, Jo BS, et al. Occupational exposure and idiopathic pulmonary fibrosis: a multicentre case-control study in Korea. *Int J Tuberc Lung Dis*. 2017;21(1):107-112.
79. Andersson M, Blanc PD, Toren K, Jarvholm B. Smoking, occupational exposures, and idiopathic pulmonary fibrosis among Swedish construction workers. *Am J Ind Med*. 2021;64:251-257.
80. Kelly-Reif K, Bertke S, Daniels RD, Richardson DB, Schubauer-Berigan MK. Nonmalignant respiratory disease mortality in male Colorado Plateau uranium miners, 1960-2016. *Am J Ind Med*. 2022;65:773-782.
81. Hnizdo E, Vallyathan V. Chronic obstructive pulmonary disease due to occupational exposure to silica dust: a review of epidemiological and pathological evidence. *Occup Environ Med*. 2003;60(4):237-243.
82. Archer VE, Renzetti A, Doggett RS, Jarvis JQ, Colby TV. Chronic diffuse interstitial fibrosis of the lung in uranium miners. *JOEM*. 1998;40(5):460-474.
83. Margaritopoulos GA, Harari S, Caminati A, Antoniou KM. Smoking-related idiopathic interstitial pneumonia: a review. *Respirology*. 2016;21:57-64.
84. Baumgartner KB, Samet JM, Stidley CA, Colby TV, Waldron JA, Collaborating Centers. Cigarette smoking: a risk factor for idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 1997;155:242-248.
85. Pauchet A, Chaussavoine A, Pairon JC, Gabillon C, Didier A, Baldi L, et al. Idiopathic pulmonary fibrosis: what do we know about the role of occupational and environmental determinants? A systematic literature review and meta-analysis. *J Toxicol Environ Health, Part B*. 2022;25(7):372-392.
86. Kaul B, Lee JS, Zhang N, Vittinghoff E, Sarmiento K, Collard HR, et al. Epidemiology of idiopathic pulmonary fibrosis among U.S. Veterans, 2010-2019. *Ann Am Thorac Soc*. 2022;19(2):196-203.
87. Kaul B, Lee JS, Glidden DV, Blanc PD, Zhang N, Collard HR, et al. Agent Orange exposure and risk of idiopathic pulmonary fibrosis among U.S. Veterans. *Am J Respir Crit Care Med*. 2022;206(6):750-757.
88. Raghu G, Chen S-Y, Maroni B, Li Q, Lee Y-C, Collard HR. Idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older: incidence, prevalence, and survival, 2001-11. *The Lancet*. 2014;2:566-572.

89. Sgalla G, Biffi A, Richeldi L. Idiopathic pulmonary fibrosis: diagnosis, epidemiology and natural history. Respirology. 2016;21:427-437.
90. Khor YH, Ng Y, Barnes H, Goh NSL, McDonald CF, Holland AE. Prognosis of idiopathic pulmonary fibrosis without anti-fibrotic therapy: a systematic review. *Eur Respir J*. 2020;29: 190158. https://doi.org/10.1183/16000617.0158-2019.
91. Lee SH, Kim DS, Kim YW, Chung MP, Take S, Park CS, et al. Association between occupational dust exposure and prognosis of idiopathic pulmonary fibrosis. A Korean national survey. *Chest*. 2015;147(2):465-474.
92. Lee CT, Adegunsoye A, Chung JH, Ventura IB, Jablonski R, Montner S, et al. Characteristics and prevalence of domestic and occupational inhalational exposures across interstitial lung diseases. *Chest*. 2021;160(1):209-218.
93. Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. Review article. *N Engl J Med*. 2018;378(19):1811-1823.
94. Dempsey TM, Sangaralingham LR, Yao X, Sanghavi D, Shah ND, Limper AH. Clinical effectiveness of antifibrotic medications for idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2019;200(2):168-174.
95. Somogy V, Chaudhuri N, Torrisi SE, Kahn N, Muller V, Kreuter M. The therapy of idiopathic pulmonary fibrosis: what is next? *Eur Respir Rev*. 2019; 28 190021 https://doi.org/10.1183/1600617.0021-2019.
96. Selman M, King TE, Pardo A, ATS; ERS; ACCP. Idiopathic pulmonary fibrosis: prevailing and evolving hypotheses about its pathogenesis and implications for therapy. Review. *Ann Intern Med*. 2001;134(2):136-151.
97. Churg A. The uptake of mineral particles by pulmonary epithelial cells. State of the Art. *Am J Respir Crit Care Med*. 1996;154:1124-1140.
98. Culver DA, Behr J, Belperio JA, Corte TJ, de Andrade JA, Flaherty KR, et al. Patient registries in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2019;200(2):160-167.
99. Nett RJ, Wood JM, Blackley DJ, NIOSH. Collecting occupational exposure data would strengthen idiopathic pulmonary fibrosis registries. Letter to the Editor. *Am J Respir Crit Care Med*. 2020; 201(4):495-496.
100. Culver DA, Kim H. Reply to Nett et al. Letter to the Authors. *Am J Respir Crit Care Med*. 2020;201(4):496.
101. Wells AU, Brown KK, Flaherty KR, Kolb M, Thannickal VJ on behalf of the IPF Consensus Working Group. What's in a name? That which we call IPF, by any other name would act the same. *Eur Respir J*. 2018; 51: 1800692 https://doi.org/10.1183/13993003.00692-2018.

TABLE 1. IDIOPATHIC PULMONARY FIBROSIS: STEPS IN PATHOGENESIS[1,24,25]

THE INFLAMMATORY THEORY – 1970s

ORIGIN: NHLBI studies showing excessive inflammatory cells in BAL of IPF patients

FALL FROM GRACE:

Poor correlation between measures of tissue inflammation and disease severity/outcome
Failure of response to anti-inflammatory medication such as corticosteroids

ALVEOLAR EPITHELIAL CELL INJURY AND ABERRANT TISSUE REPAIR FOLLOWING MULTIPLE EPISODES OF LUNG INJURY – 1980s

ORIGIN: Ultrastructural studies of the lungs of IPF patients showing

1. Type I alveolar-epithelial cell injury
2. Damage to the alveolar epithelial-capillary endothelial BM with failure of reepithelialization and reendothelialization of BMs leading to
3. Loss of the integrity of the alveolar-capillary BM
4. Intra-alveolar deposition of ECM and accumulation of fibroblasts and myofibroblasts
5. Fusion of adjacent alveolar-capillary BMs and development of fibroblastic foci

ADDITIONAL CONCEPTUAL MECHANISMS:

6. Aberrant tissue repair with destruction of normal architecture and development of fibrosis
7. Persistent antigen/irritant microinjury driving the propagation of fibrosis
8. Promotion of permanent fibrosis by production of cytokines such as TGF-β
9. EMT and fibroblast recruitment from bone marrow progenitor cells

---

NHLBI – U.S. National Heart Lung Blood Institute; BAL – bronchoalveolar lavage; BM – basement membrane; ECM – extracellular matrix; TGF – transforming growth factor; EMT – epithelial to mesenchymal cell transition

---

TABLE 2. OCCUPATIONAL CAUSATION IN IPF: STATISTICALLY SIGNIFICANT EXPOSURE ASSOCIATIONS

OCCUPATION/INDUSTRY	EXPOSURE	
	ORGANIC	INORGANIC
Agriculture, livestock[20,21,63]	Vegetable, animal dust, feed grains	
Asbestos imports, mining, manufacturing[72-74]		Asbestos dust/fibres
Carpentry, cabinet maker, woodworker[44,50,53,56]		Wood dust
Domestic, hobbies[21,56]	Birds	
Metal worker, metallurgical or steel industry, machine operator, metal mining[21,44,50,53,54,78]		Metal dust, fume
Mining, construction, manufacturing, foundries[75]		Respirable dust
Stone cutting, polishing[20,44,49,63]		Stone, sand, silica
Vapors, gases, dust, fumes[30]		Dusts, smokes, gases, chemicals
Workplace NOS[49]	Mould/mildew	