Idiopathic Pulmonary Fibrosis: Diagnosis and Epidemiology

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KEYWORDS

• Idiopathic pulmonary fibrosis • Diagnosis
• Epidemiology • Treatment

Idiopathic pulmonary fibrosis (IPF) is defined as a chronic fibrosing interstitial pneumonia of unknown cause with a histologic pattern of usual interstitial pneumonia (UIP) on surgical lung biopsy. IPF is a lung-limited process that tends to occur in older adults. It is the most common of the idiopathic interstitial pneumonias (IIPs), among which it has the worst prognosis, with median survival estimates ranging from 3 to 5 years after diagnosis.[1–3]

In 2000, the American Thoracic Society (ATS) and European Respiratory Society (ERS) published the first consensus statement providing guidelines on the diagnosis and treatment of IPF.[1] This statement presented, for the first time, diagnostic criteria for IPF and recommendations for treatment. Over the past decade, results from several studies have reshaped the thinking on IPF, and as a result, the guidelines have been recently revised using an evidence-based approach.[2] Meanwhile, several epidemiologic studies have yielded data that identify potential risk factors and that better define the societal burden of IPF. This article summarizes the approach to diagnosing IPF and reviews epidemiologic data on IPF.

THE DIAGNOSIS OF IPF

Over the past decade, emerging data have helped to refine the diagnostic criteria for IPF. In 2000, a collaborative effort among the ATS, ERS, and American College of Chest Physicians resulted in an international consensus statement for the diagnosis of IPF.[1] That statement, formulated on expert opinion and interpretation of available research at the time, held that a definitive diagnosis of IPF required a surgical lung biopsy showing a UIP pattern of lung injury and the following 3 criteria: (1) exclusion of other known causes of interstitial lung disease (ILD), including drug toxicities, environmental exposures, and collagen vascular diseases; (2) abnormal pulmonary function tests or impaired gas exchange; and (3) imaging consistent with this diagnosis. In the absence of a surgical lung biopsy, a diagnosis of probable IPF required all of the following 4 major criteria: (1) exclusion of other causes of ILD; (2) abnormal pulmonary function tests or impaired gas exchange; (3) bibasilar reticular abnormalities with minimal ground-glass opacities on high-resolution computed tomography (HRCT); and (4) transbronchial lung biopsy or bronchoalveolar lavage specimens without features to support an alternative diagnosis along with at least 3 of 4 minor criteria (age >50 years, the insidious onset of dyspnea, a duration of symptoms greater than 3 months, and bibasilar, inspiratory crackles).

Since that time, additional evidence has shown the value of HRCT in diagnosing IPF: when an experienced radiologist can say with high confidence that the pattern on HRCT is consistent with a histologic UIP pattern, UIP is the histologic pattern identified in more than 90% of cases.[4–7] Based on these and other data supporting the accuracy of HRCT, a surgical lung biopsy is no longer required for a definitive diagnosis of IPF in

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cases with a radiologic UIP pattern and a compatible clinical presentation,[3] and the characteristic HRCT pattern of a UIP pattern of lung injury has been defined (**Box 1**). Given a characteristic HRCT pattern, the diagnosis of IPF still requires exclusion of other known causes of ILD, including domestic, occupational, or environmental exposures, connective tissue diseases, and drug toxicities.

For diagnosing IPF, the sensitivity of HRCT is significantly lower than its positive predictive value[4–9]; thus, when the characteristic HRCT pattern is absent, a surgical lung biopsy showing a UIP pattern is still required to make a definitive diagnosis of IPF.[3] Histologic criteria have been devised to allow pathologists to categorize findings in surgical lung biopsy specimens as definite, possible, probable, or not UIP (**Box 2**). In addition, the recently published evidence-based guidelines provide a framework for interpreting permutations of HRCT and histologic data (**Table 1**).

Box 1
Criteria for a definite, possible, and inconsistent UIP pattern on HRCT scan

Definite UIP Pattern (requires all 4 of the following features)

Subpleural, basal predominance

Reticular abnormality

Honeycombing without traction bronchiectasis

Absence of features that are inconsistent with a UIP pattern (see "Possible UIP Pattern")

Possible UIP Pattern

Same as the criteria for a definite UIP pattern, although honeycombing is not present

Inconsistent with UIP Pattern (any of the following 7 features)

Upper-lung or midlung predominance

Peribronchovascular predominance

Extensive ground-glass abnormality (defined as the extent of the ground-glass abnormality is greater than the extent of the reticular abnormality)

Profuse micronodules

Discrete cysts

Diffuse mosaic attenuation or air-trapping (bilateral, in 3 of more lobes)

Consolidation in bronchopulmonary segments or lobes

Data from American Thoracic Society; European Respiratory Society. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med 2001;165:277–304.

Challenges in Diagnosing IPF

A threat to making a confident diagnosis of IPF arises when, as is the case in 12.5% to 26% of patients who have a multilobe surgical lung biopsy, a UIP pattern is found in samples from 1 lobe, but a different pattern is found in samples from another lobe (a scenario termed discordant UIP).[10,11] However, survival in patients with discordant UIP is similar to patients with concordant UIP (ie, surgical lung biopsy samples from all lobes having UIP patterns).[10,12] Thus, if a surgical lung biopsy is performed, multiple lobes should be sampled, and a diagnosis of definite IPF can be made when a UIP pattern is identified in any lobe (regardless of what is found in any other sample).

Making a diagnosis of IPF can be difficult, but the accuracy and confidence of an IPF diagnosis increases with multidisciplinary discussions among clinicians, radiologists, and pathologists. In a study of 58 consecutive cases of suspected IIP, Flaherty and colleagues[13] sequentially gave expert clinicians, radiologists, and pathologists more and more information about a case of ILD, and then allowed them to discuss their impressions as a group. As more information was divulged and cross-disciplinary discussions took place, the level of agreement about the diagnosis (and the degree of certainty in that diagnosis) improved. Not surprisingly, centers with expertise in IPF are more accurate at diagnosing IPF than community-based, referral practices.[5] For unclear reasons, early referral to such a center seems to improve survival in patients with IPF.[14]

THE EPIDEMIOLOGY OF IPF

Background

Epidemiology is defined as "the study of the distribution and determinants of health-related states or events (including disease)," and the goal of epidemiologists is to apply findings to control diseases or health issues.[15–17] Specific objectives include determining the extent and effects of disease: by defining its prevalence, incidence, and mortality; by identifying its risk factors or causes; and by examining its natural history and prognosis. This information then allows for the evaluation of preventative and therapeutic interventions, and builds a foundation for policies and regulatory decisions to be made that alleviate the burden of disease.[17]

The relative rarity of IPF has challenged investigators with an interest in its epidemiology, and

Box 2
Criteria for a definite, probable, possible, and inconsistent UIP pattern based on surgical lung biopsy

Definite UIP Pattern (requires all 4 of the following features)

Evidence of fibrosis/architectural distortion with or without honeycombing in a predominantly subpleural/paraseptal location

Fibrosis in a patchy distribution

Fibroblast foci

Absence of features suggesting a not UIP pattern (see "Not UIP Pattern")

Probable UIP Pattern (requires either the first 3 criteria of the fourth criteria)

Evidence of fibrosis/architectural distortion with or without honeycombing in a predominantly subpleural/paraseptal location

Either fibrosis in a patchy distribution or fibroblast foci

Absence of features suggesting a not UIP pattern (see "Not UIP Pattern")

Honeycomb changes alone

Possible UIP Pattern

Patchy or diffuse involvement with fibrosis with or without interstitial inflammation

Absence of features suggesting a not UIP pattern (see "Not UIP Pattern")

Not UIP Pattern

Hyaline membranes or organizing pneumonia (unless associated with an acute exacerbation of IPF)

Organizing pneumonia or granulomas (unless mild or occasional, respectively, but may otherwise suggest hypersensitivity pneumonitis)

Marked interstitial inflammation away from honeycombing

Predominant airway-centered disease

Other features suggesting an alternative diagnosis

Data from American Thoracic Society; European Respiratory Society. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med 2001;165:277–304.

before 1990, discouraged large-scale epidemiologic studies from being performed.[18] Although Leibow and Carrington first defined a UIP pattern

Table 1
Criteria for a definite, probable, and possible diagnosis of IPF based on both HRCT pattern and surgical lung biopsy findings

HRCT Pattern	Surgical Lung Biopsy Pattern	Diagnosis of IPF
UIP	UIP	IPF
	Probable UIP	IPF
	Possible UIP	IPF
	Nonclassifiable fibrosis	IPF
	Not UIP	Not IPF
Possible UIP	UIP	IPF
	Probable UIP	IPF
	Possible UIP	Probable IPF
	Nonclassifiable fibrosis	Probable IPF
	Not UIP	Not IPF
Inconsistent with UIP	UIP	Possible IPF
	Probable UIP	Not IPF
	Possible UIP	Not IPF
	Nonclassifiable fibrosis	Not IPF
	Not UIP	Not IPF

Data from American Thoracic Society; European Respiratory Society. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. Am J Respir Crit Care Med 2001;165:277–304.

in 1969,[19] IPF was not given a diagnostic code in the International Classification of Diseases (ICD) until the ninth revision (ICD-9) at the end of the 1970s.[20] This coding system gave investigators an opportunity to use ICD-coded mortality data to study the burden of IPF at the population level. Johnston and colleagues[21] did so, and published their results of mortality (discussed later) in 1990.

Mortality and Mortality Trends Over Time

Disease-specific mortality is calculated by determining the number of deaths per year resulting from a specific cause, divided by the number of persons alive in the midyear population. In a disease that is lethal, and when survival is short, as occurs in IPF, mortality serves as a surrogate for the incidence of disease.[17]

Death certificate and census data are vital statistics recorded in several countries, and these data have provided investigators with the means to study mortality and mortality trends over time. Little

is known about the validity of death certificate ICD coding in IPF, so results from studies using death certificate data should be interpreted with some caution. Investigators in the United Kingdom found that in 23 decedents with a diagnosis of IPF (ICD-9 code 516.3) recorded on a death certificate, 19 (83%) had premortem clinical information confirming either definite or possible IPF.[21] Conversely, among 45 patients with a premortem diagnosis of IPF (ICD-9 code 516.3), IPF was recorded on the death certificate only about 50% of the time. Before the ICD-10 coding system (which combines IPF and postinflammatory pulmonary fibrosis [PIPF]),[22] diagnostic transfer (or coding IPF as PIPF on the death certificate) was also reported to occur commonly. Of 20 decedents coded with PIPF (ICD-9 code 515) on the death certificate, nearly 50% had IPF (ICD-9 code 516.3) diagnosed before death. These data suggest IPF is likely underrecorded as the cause of death, and a significant proportion of decedents coded as dying from PIPF died of IPF. Although these findings are based on a small number of decedents from the United Kingdom, Coultas and Hughes[23] identified similar issues in mortality data from New Mexico.

Because the ICD-10 coding system combined PIPF and IPF into 1 diagnostic code (J84.1),[22] researchers calculating mortality with data after 1998 are likely including some decedents with progressive, fibrosing ILD that is not IPF. Investigators who have used this diagnostic code (J84.1) and who have systematically excluded cases with known-cause pulmonary fibrosis (PF) have termed this entity general PF.[24,25] Other investigators have not excluded concurrent conditions that may result in PF, and have termed this entity IPF clinical syndrome (IPF-CS).[26] Regardless of the precise diagnosis (ie, IPF vs other progressive, fibrotic ILD) for decedents in such studies, trends in mortality reveal that PF is a daunting and growing public health problem.[24–26]

Johnston and colleagues[21] were the first to calculate IPF (previously termed cryptogenic fibrosing alveolitis in the United Kingdom) mortality in a large-scale epidemiologic study. They found that in England and Wales, from 1979 to 1988, deaths from IPF (ICD-9 code, 516.3) more than doubled. IPF-associated mortality was more common in men (odds ratio [OR] = 2.24; 95% confidence interval [CI] = 2.11–2.38) and increased progressively with age: the risk of IPF in those 75 years old or older was 8 times the risk for those 45 to 54 years old. Greater mortality was found in the central, industrialized areas of England and Wales, suggesting environmental/occupational exposures could be a risk factor for IPF.

Hubbard and colleagues[27] extended on the work of Johnston and colleagues by investigating available mortality data for both IPF (ICD-9 code 516.3) and PIPF (ICD-9 code 515) from England, Wales, Scotland, Germany, Australia, New Zealand, Canada, and the United States from 1979 to 1992. They found that mortality from IPF was the highest in England and Wales and rates were increasing not only in these countries but also in Scotland, Australia, and Canada. Mortality from IPF was stable in New Zealand and Germany and had decreased over time in the United States. Mortality from PIPF was the highest in the United States, and increased over the study period in the United States, the United Kingdom, Canada, and Australia, with stable mortality again noted in New Zealand and Germany. The increase in mortality from PF could not be explained by diagnostic transfer (eg, a change in coding practices from PIPF to IPF, or PIPF to IPF over time), although systematic diagnostic transfer (always coding IPF as PIPF, because of different terminology and coding rules)[24] may have explained the higher mortality of PIPF in the United States.

Mannino and colleagues[24] examined PF mortality data in the United States from 1979 to 1991. To capture all decedents with IPF, given the coding issues noted earlier, these investigators defined PF by combing ICD-9 diagnostic codes 515 (PIPF) and 516.3 (IPF) and eliminated cases with concurrent diagnostic codes for conditions with known associations with PF, including radiation fibrosis, collagen vascular diseases, or asbestosis. Over that 13-year period, age-adjusted mortality from PF increased 4.7% in men (from 48.6 per million to 50.9 per million) and increased 27.1% in women (from 21.4 per million to 27.2 per million). PF-associated mortality increased with increasing age. States with the highest PF-associated mortality were in the west and southeast, and those with the lowest rates were in the midwest and northeast.

Data from the 1990s to early 2000 show a further increase, and acceleration, in PF-associated mortality. Using US mortality data from 1992 to 2003 and applying methods similar to Mannino and colleagues, Olson and colleagues[25] analyzed more than 28 million death records and found that the age-adjusted and standardized (to the year 2000) mortality increased 29.4% in men (from 49.7 deaths per million to 64.3 deaths per million) and 38.1% in women (from 42.3 deaths per million to 58.4 deaths per million) (**Fig. 1**). Rates increased with increasing age. Compared with the previous decade, mortality over this period increased at a significantly faster pace in both men and women. From 1992 to 2003, rates

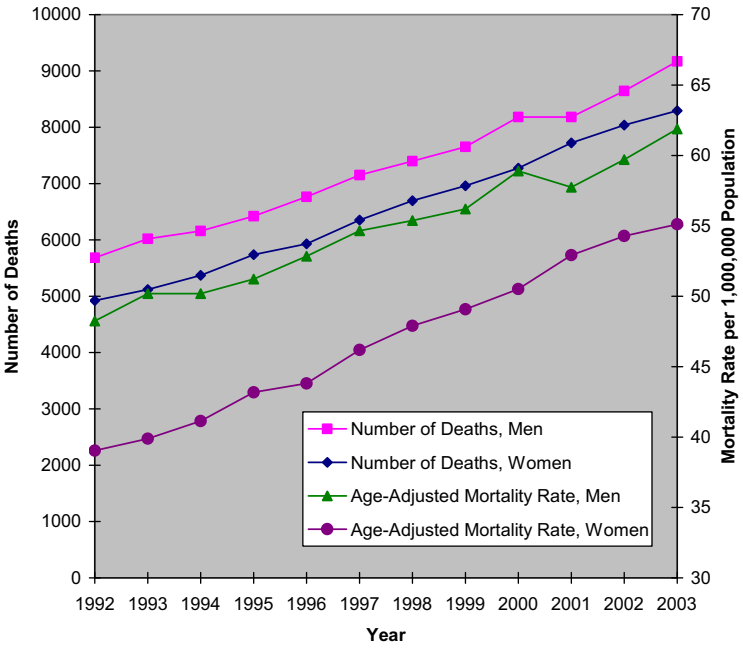

Fig. 1. Number of deaths per year and age-adjusted mortality in decedents with PF per 1,000,000 population from 1992 to 2003 in the United States. Mortality is standardized to the 2000 US census population. (*Reproduced from* Olson AL, Swigris JJ, Lezotte DC, et al. Mortality from pulmonary fibrosis increased in the United States from 1992 to 2003. Am J Respir Crit Care Med 2007;176:278; with permission.)

rose more steeply in women than men. Mortality was greater among white non-Hispanics than black non-Hispanics or Hispanics, suggesting that race and ethnicity may also play a role in the susceptibility to IPF.

Similar trends were recently reported in the United Kingdom: age-adjusted and sex-adjusted mortality from IPF-CS (ICD-9 code 515 or 516.3, or ICD-10 code J84.1) have reached 51 per million person-years (an increase of 5% per year since the late 1960s).[26] These studies suggest that, although once considered an orphan disease, PF (and PF-associated mortality) is more common than several common malignancies and is an important public health concern, particularly in elderly people.[25,26]

Prevalence and Incidence, and Trends Over Time

The prevalence of disease is defined as the number of persons with disease at a specific point in time divided by the total population at that time, and incidence is defined as the number of persons with newly diagnosed disease divided by the number of persons at risk for developing that disease over that period of time. Prevalence is a proportion; incidence is a rate. In disease processes in which the incidence and the duration of the disease are stable, the prevalence should reflect the incidence multiplied by the duration of the disease.[28]

Before 1994, little was known about the incidence or prevalence of ILD in general or IPF in particular.[29–31] Coultas and colleagues[32] performed one of the first large-scale epidemiologic investigations to determine the prevalence and incidence of IPF. Using several, broad case-finding methods, they established a population-based registry of ILD in Bernalillo County, New Mexico. From 1988 to 1993, they found that IPF was the most common ILD in this region, accounting for 22.5% of prevalent cases and 31.2% of incident cases. The prevalence and incidence of IPF was higher in men (20.2 cases per 100,000 persons and 13.2 cases per 100,000/y, respectively) than women (10.7 per 100,000 persons and 7.4 per 100,000/y, respectively). Both the prevalence and incidence of IPF increased dramatically with age (**Table 2**). Limitations to this study included that these data came from only 1 county in New Mexico, so it was not known whether these were applicable to the United States as a whole.

More than a decade later, Raghu and colleagues[33] determined the prevalence and incidence of IPF using a large health care claims database from a US health plan that covered approximately 3 million persons in 20 states. Using data from 1996 to 2000, they determined the prevalence and incidence of IPF using both a narrow and broad definition of IPF. The broad definition of IPF included any person 18 years of age or older, with 1 or more medical claims with a diagnosis of IPF (ICD-9 of 516.3), and without any other medical claims for a diagnosis of another ILD on or after the date of the last medical claim with

Table 2
The prevalence and incidence of IPF by age strata and gender in Bernalillo County, New Mexico from 1988 to 1993

	IPF (Prevalence, per 100,000 Persons)		IPF (Incidence, per 100,000 Persons/y)	
Age Strata (y)	Men	Women	Men	Women
35–44	2.7	–	4.0	–
45–54	8.7	8.1	2.2	4.0
55–64	28.4	5.0	14.2	10.0
65–74	104.6	72.3	48.6	21.1
≥75	174.7	73.2	101.9	57.0

Data from Coultas DB, Zumwalt RE, Black WC, et al. The epidemiology of interstitial lung diseases. Am J Respir Crit Care Med 1994;150:967–72.

this diagnostic code for IPF. The narrow definition of IPF included those criteria plus at least 1 claim for either a procedure code for surgical or transbronchial lung biopsy or a computed tomography scan of the thorax. They found that the overall prevalence of IPF was 14.0 or 42.7 per 100,000 persons, depending on whether the narrow or broad case definitions were used. These investigators found that the incidence of IPF was 6.8 or 16.3 per 100,000 persons per year, depending on whether the narrow or broad case definitions were used. Similar to Coultas and colleagues, they also found that both the prevalence and incidence increased with age (**Table 3**). Compared with Coultas and colleagues, Raghu and colleagues calculated prevalence and incidence estimates that were greater, suggesting the burden of disease had increased over time (see **Tables 2** and **3**).

Studies performed outside the United States also suggest that the incidence of IPF has increased over time. Using a general practice database in the United Kingdom, Gribbin and colleagues[34] examined persons with a diagnosis of IPF from 1991 to 2003. During this period, the overall incidence of IPF was 4.6 per 100,000 person-years (numbers slightly lower than reported by either Coultas and colleagues or Raghu and colleagues). However, this study suggested that the burden of IPF had increased over time: the incidence had more than doubled, a finding not explained by an aging population.

Similar to the case with mortality, it is unclear if these reported increases in incidence represent a true increase in disease occurrence or simply improved recognition of the disease. Case ascertainment may have increased over this period because of a growing use of HRCT in the evaluation of ILD. Increased public and community practice awareness of IPF may also account for these trends: during the 1990s, the first large, multicenter, therapeutic trial for IPF was conceptualized and began enrolling patients.[35]

Navaratnam and colleagues[26] reexamined the trends in incidence of PF in the United Kingdom through 2008. Using computerized primary care

Table 3
The prevalence and incidence of IPF by age strata and gender from a health care claims processing system of a large US health plan from 1996 to 2000 using the broad case definition (please see text)

	IPF (Prevalence, per 100,000 Persons)		IPF (Incidence, per 100,000 Persons/y)	
Age Strata (y)	Men	Women	Men	Women
35–44	4.9	12.7	1.1	5.4
45–54	22.3	22.6	11.4	10.9
55–64	62.8	50.9	35.1	22.6
65–74	148.5	106.7	49.1	36.0
≥75	276.9	192.1	97.6	62.2

Data from Raghu G, Weycker D, Edelsberg J, et al. Incidence and prevalence of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2006;174:810–16.

records in the United Kingdom, they found that the incidence of IPF-CS (defined from 1965 to 1978 as ICD, eighth edition code 517, from 1979 to 1999 as ICD-9 code 516.3 and 515, and from 2000 onward as ICD-10 code J84.1) increased at a rate of approximately 5% per year.

Data from the United States, published within the past year, suggested a different trend. Fernandez-Perez and colleagues[36] analyzed data from Olmsted County, Minnesota to determine incidence and prevalence of IPF from 1997 to 2005. They screened 596 patients in a population-based registry for PF. Overall, the age-adjusted and sex-adjusted incidence was 8.8/100,000 person-years based on a narrow-case definition of IPF (UIP pattern on surgical lung biopsy or characteristic HRCT), and 17.4/100,000 person-years based on a broad case definition (UIP pattern on surgical lung biopsy or either definite or possible characteristic HRCT). The incidence was higher in men than in women, and the incidence increased with advancing age in men, and until the age of 80 years in women. Unlike any of the other investigators whose studies were described earlier, Fernandez-Perez and colleagues observed that the incidence significantly ($P<.001$) decreased over the study period (although peaks in incidence were noted in 1998 and 2001). In 2005, the age-adjusted and sex-adjusted prevalence of IPF was 27.9/100,000 and 63/100,000 (using the narrow and broad definition, respectively). However, given the aging population, these investigators project that the annual number of newly diagnosed cases of IPF in the US population by 2050 may reach 21,000. It is impossible to speculate whether these trends, observed in this 1 county, reflect the most current trends at a national or international level.

Risk Factors

Although IPF is defined as an idiopathic disease, epidemiologic studies have identified several risk factors (including environmental and occupational exposures) associated with the diagnosis. These studies tend to be case-control studies and are subject to bias: recall bias occurs when persons with disease recall exposures differently from those without the disease, and diagnosis misclassification bias occurs when the number of individuals incorrectly diagnosed with IPF is not equally distributed between those with and those without the risk factor.[37] Also, in case-control studies, the accurate assessment of dose and duration of exposure is challenging; thus, identifying a dose-response effect of the risk factor is frequently impossible.[38] Although case reports also suggest associations between IPF and several different exposures, the following discussion of exposures is limited to those in which the exposure was identified in 2 or more independent studies or via a meta-analysis. Clinical factors, including gastroesophageal reflux disease, diabetes, and infectious agents have been implicated as risk factors for IPF, but are beyond the scope of this review.[3]

Cigarette smoking

Several case-control studies have yielded data on the association between IPF and smoking. Baumgartner and colleagues[39] identified 248 IPF cases from 16 referral centers in the United States and matched these cases to 491 control individuals on sex, age, and geography. A smoking history was more common in those with IPF (72%) than controls (63%) (OR = 1.6; 95% CI = 1.1–2.4). Three other case-control studies from the United Kingdom and Japan found a similar association.[40–42] Scott and colleagues[30] found no association between IPF and smoking in a case-control study of 40 patients with IPF from Nottingham, United Kingdom and 106 matched controls. Of all the studies on the topic, this one included the fewest cases. In a meta-analysis of these 5 studies, patients with IPF were significantly more likely than controls to report a smoking history (OR = 1.58; 95% CI = 1.27–1.97).[38]

In an attempt to identify a dose-response relationship between smoking and IPF, Baumgartner and colleagues[39] observed that, when compared with individuals who had a 20–pack-year or fewer smoking history, those with a 21–pack-year to 40–pack-year history had a greater odds of developing IPF (OR = 2.26; 95% CI = 1.3–3.8); however, for those with a history greater than 40 pack-years, there was no further increase in the risk of developing IPF (OR = 1.12; 95% CI = 0.7–1.9). After adjusting for age, sex, and region of residency, Miyake and colleagues[42] found an association between IPF and smoking in those with a 20–pack-year to 39.9–pack-year history (OR = 3.23; 95% CI = 1.01–10.84), but not for those with either a fewer or greater pack-year history.

Environmental and Occupational Exposures

Because other environmental exposures (including asbestosis, silicosis, and coal workers' pneumoconiosis) are known to cause fibrotic lung disease,[43–45] IPF is more likely to occur in men than women (and men are more likely than women to work in jobs in which such exposures occur),[2] and IPF-associated mortality is higher in highly industrialized regions of some countries,[21] it has been hypothesized that environmental or occupational exposures may also be associated with IPF.

Metal dust

In several case-control studies and a meta-analysis, investigators have examined the association between a variety of environmental or occupational exposures and the risk of IPF. Each of the initial 5 studies yielded data that suggested an association between metal dust exposure and IPF (OR from the meta-analysis = 2.44, 95% CI = 1.74–3.40).[30,38,40–42,46] In 2 of these studies, a dose-response relationship was found.[40,46] In further support of this association, elemental microanalyses of hilar and mediastinal lymph nodes in patients with IPF have shown increased nickel,[47] silicon,[48] and aluminum[48] levels compared with controls.

In contrast, Gustafson and colleagues[49] recently found no association between metal dust exposure and IPF (OR = 0.9; 95% CI = 0.51–1.59) among 140 patients IPF and 757 matched controls in Sweden; they did not assess for a dose-response relationship.

Hubbard and colleagues[50] assembled a historical cohort from the pension-fund archives of employees who had worked for Rolls-Royce plc in the United Kingdom to determine the risk of IPF in those exposed to metal dust. Among members of this cohort, there were 20,526 total deaths, and 55 were IPF associated. The number of IPF-associated deaths in this cohort was significantly greater than expected based on national mortality (proportional mortality ratio = 1.39; 95% CI = 1.07–1.82). Among the 22 decedents with available archive data, a dose-response relationship between metal exposure and IPF was identified (OR per 10 years of exposure = 1.71; 95% CI = 1.09–2.68).

Using US death certificate data from 1999 to 2003 and available industry/occupation codes for a proportion of decedents with PF (ICD-10 code J84.1), Pinheiro and colleagues[51] found an increase in the proportionate mortality (PM) for those decedents whose industry was recorded as metal mining (PM = 2.4; 95% CI = 1.3–4.0) and those whose industry was recorded as fabricated structural metal products (PM = 1.9; 95% CI = 1.1–3.1).

Wood dust

In the studies mentioned earlier, and other case-controlled studies, researchers have examined the association between wood dust exposure and IPF.[30,38,40,42,46,52] Of the initial 5 studies, in only one did investigators observe a significantly increased risk of IPF in patients exposed to wood dust (OR = 1.71; 95% CI = 1.01–1.92).[40] However, when all of these studies were included in a meta-analysis, an increased risk of IPF was found in patients with exposure to wood dusts (OR = 1.94; 95% CI = 1.34–2.81).[38] In another study from Sweden, not included in the meta-analysis, there was no association between any wood dust and IPF among the entire study sample (OR = 1.2; 95% CI = 0.65–2.23); however, there was an increased risk of IPF in men exposed to birch dust (OR = 2.7, 95% CI = 1.30–5.65) or hardwood dust (OR = 2.7; 95% CI =1.14–6.52). No association between IPF and fur or fir dust was identified. This finding suggests that in addition to gender, specific types of dust may play a role in the pathogenesis of IPF.[49]

Sand, stone, and silica

Three of 4 case-control studies have found an increased risk of IPF in patients with exposures to sand, stone, or silica, with a summary OR of 1.97 (95% CI = 1.09–3.55).[30,38,40,46,52]

Farming and livestock

Agriculture/farming-related and livestock-related exposures have been found to be associated with IPF. In 2 case-control studies, 1 from the United States and 1 from Japan, workers in the agriculture or farming sectors were found to have an increased risk of IPF (meta-analysis OR = 1.65, 95% CI = 1.20–2.26).[38,41,46] The 1 study noted earlier from the United States and another study from the United Kingdom both found that exposure to livestock was associated with an increased risk of IPF (meta-analysis OR = 2.17, 95% CI = 1.28–3.68).[30,38,46] Further, Baumgartner and colleagues[46] identified a dose-response relationship between livestock exposure and IPF. After adjusting for age and smoking history, they found no increased risk for IPF among patients exposed for less than 5 years (OR = 2.1; 95% CI = 0.7–6.1), but a significantly increased risk for IPF among those with 5 or more years of exposure (OR = 3.3; 95% CI = 1.3–8.3).

SUMMARY

Over the last decade or two, results from several studies have advanced understanding of IPF: how it is diagnosed, its basic epidemiologic profile, and occupational or environmental exposures that may increase the risk for developing the disease. These results have reshaped how IPF is diagnosed, especially by highlighting the accuracy with which a characteristic HRCT identifies a UIP pattern of lung injury: patients with such an HRCT need not have a surgical lung biopsy for IPF to be diagnosed confidently. However, making a diagnosis of IPF is complex, and whether a surgical lung biopsy is indicated or not, diagnostic accuracy is improved with multidisciplinary discussions in

centers that specialize in the care of patients with this disease. Over the same period, the burden of IPF seems to have increased, with some incidence and mortality estimates placing IPF on par with certain relatively common malignancies. Although through case-control and cohort studies investigators have identified risk factors for IPF, these studies do not prove causality, and further research is needed not only to better understand the underlying pathobiology of this complex disease but also to find effective therapies for it.

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