Chapter 2
Idiopathic Pulmonary Fibrosis: The Epidemiology and Natural History of Disease

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Introduction

Idiopathic pulmonary fibrosis (IPF) has been classically described as a disease that progresses in a "relentless and often insidious manner," with median survival estimates of 2–3 years from the time of diagnosis [1, 2]. However, research over the past two decades has improved our understanding of the natural history of IPF. Although some patients experience steadily progressive respiratory decline, it is now recognized that the clinical course for others is marked by rapid progression and/or acute episodes of worsening that not infrequently result in death. At the group level, clinical factors associated with an increased risk of mortality have been identified, but predicting the course of disease in an individual patient is challenging, if not impossible. Whether differences in the clinical course result from varying phenotypes of IPF or from other factors (e.g., differences in the type, degree, or intensity of environmental exposures or ethnic and racial differences) is unclear [2, 3]. While certain investigators were generating research that refined understanding of how IPF behaves over time, others were performing epidemiologic studies that better defined the societal burden of IPF and identified environmental exposures associated with an increased risk for developing the disease. In this chapter, we review recently acquired epidemiologic data on IPF and describe the variable natural history of a disease that continues to confound clinicians and researchers alike.

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The Epidemiology of IPF

Background

Investigators have used epidemiologic studies to determine the societal burden of IPF and to identify possible exposures and risk factors (predominantly through case-control studies) for disease development. These studies have revealed that IPF is not as rare as it was once believed to be, underscoring the need for more resources to advance research for this devastating condition. Results from additional epidemiologic studies have identified specific risk factors for IPF, providing insight into possible pathobiologic mechanisms for disease. Hopefully, these studies will prove useful as investigators search for approaches to limit disease occurrence [4].

Prior to the 1990s, factors that kept investigators from conducting large-scale epidemiologic studies in IPF included the supposed rarity of disease, the evolving (changing) case definition of IPF, and the lack of a specific International Classification of Diseases (ICD) diagnostic code. Since then, three developments have changed the landscape of epidemiologic research in IPF: (1) the ninth revision of the ICD coding (ICD-9) system (which for the first time assigned a diagnostic code for IPF and occurred at the end of the 1970s), (2) large population databases (including death certificate data and healthcare claims data), and (3) both regional and multicenter collaborative efforts to determine both the extent of and risk factors for disease.

Prevalence, Incidence, and Secular Trends

Prevalence is a ratio defined as the number of persons with a disease at a specific point in time divided by the total population at that time. Incidence is a rate, defined as the number of new cases (that have developed over a given period of time) divided by the number of persons at risk for developing disease over that period of time.

Coultas and colleagues performed the first regional epidemiologic investigation in the United States to determine the prevalence and incidence of interstitial lung disease (ILD) [5]. Using multiple case-finding methods (including primary care and pulmonary physician's records, histopathology reports, hospital discharge diagnoses, death certificates, and autopsy reports), these investigators established a population-based ILD registry in Bernalillo County, New Mexico – a county with a population of nearly one-half million at the time of this study. Based on data from 1988 to 1993, the overall prevalence of IPF was 20.2 cases per 100,000 men and 13.2 cases per 100,000 women. When these data were stratified by age and gender, the prevalence of IPF increased with increasing age and was higher for men than for women in each age strata (Table 2.1). The incidence of IPF was 10.7 per 100,000 persons/year in men and 7.4 per 100,000 persons/year in women. Again, when stratified by age and gender, the incidence of IPF generally increased with increasing age and was typically higher for men than for women (Table 2.2).

Table 2.1 The prevalence of IPF by age strata and gender in Bernalillo County, New Mexico, from 1988 to 1993 [5] compared to a healthcare claims processing system of a large US health plan from 1996 to 2000 using the broad case definition [6] (see text)

Idiopathic pulmonary fibrosis (prevalence, per 100,000 persons)				
	1988–1993		1996–2000	
Age strata (years)	Men	Women	Men	Women
35–44	2.7	–	4.9	12.7
45–54	8.7	8.1	22.3	22.6
55–64	28.4	5.0	62.8	50.9
65–74	104.6	72.3	148.5	106.7
≥75	174.7	73.2	276.9	192.1

Adapted from Table 4 in [5] and Fig. 1 in [6]

Table 2.2 The incidence of IPF by age strata and gender from Bernalillo County, New Mexico, from 1988 to 1993 [5] compared to a healthcare claims processing system of a large US health plan from 1996 to 2000 using the broad case definition [6] (see text)

Idiopathic pulmonary fibrosis (incidence, per 100,000 persons/year)				
	1988–1993		1996–2000	
Age strata (years)	Men	Women	Men	Women
35–44	4.0	–	1.1	5.4
45–54	2.2	4.0	11.4	10.9
55–64	14.2	10.0	35.1	22.6
65–74	48.6	21.1	49.1	36.0
≥75	101.9	57.0	97.6	62.2

Adapted from Table 5 in [5] and Fig. 2 in [6]

Raghu and colleagues determined the prevalence and incidence of IPF from 1996 to 2000 using data from a large US healthcare plan's claims system [6]. Using a broad definition for IPF (age >18 years, one or more medical encounters coded for IPF, and no medical encounters after that IPF encounter with a diagnosis code for any other type of ILD), these investigators estimated the prevalence and annual incidence of the disease to be 42.7 and 16.3 per 100,000 people, respectively. A narrow case definition (broad definition plus at least one medical encounter with a procedure code for a surgical lung biopsy, transbronchial biopsy, or computed tomography [CT] of the thorax) yielded a prevalence and annual incidence of 14.0 per 100,000 people and 6.8 per 100,000 people, respectively. In their dataset both prevalence and incidence increased with increasing age, and rates were higher in men than women (see Tables 2.1 and 2.2). Results from these two studies suggest that rates have increased over time; however, their limitations constrain these studies as only being hypothesis-generating.

Fernández-Pérez and colleagues performed a population-based, historical cohort study in Olmsted County, Minnesota, of patients evaluated at their center between 1997 and 2005. They had three aims for their study: (1) determine the prevalence and incidence of IPF, (2) determine if incidence changed over time, and (3) predict

the future burden of disease [7]. For 2005, using narrow case-finding criteria (usual interstitial pneumonia [UIP] pattern on surgical lung biopsy or definite UIP pattern on high-resolution CT [HRCT]), the age- and sex-adjusted prevalence (for people over the age of 50 years) was 27.9 cases per 100,000 persons (95% CI = 10.4–45.4); using broad case-finding criteria (UIP pattern on surgical lung biopsy or definite *or possible* UIP pattern on HRCT), it was 63 cases per 100,000 persons (95% CI = 36.4–89.6). Over the 9 years of this study, the age- and sex-adjusted incidence (for those over the age of 50) was 8.8 cases per 100,000 person-years (95% CI = 5.3–12.4) and 17.4 cases per 100,000 person-years (95% CI = 12.4–22.4) for the narrow and broad case-finding criteria, respectively. In contrast to the incidence rates reported by Coultas and Raghu [5, 6], results here suggest significantly decreasing incidence rates over the last 3 years of the study to 6.0 or 11.0 per 100,000 person-years using the narrow or broad case-finding criteria, respectively ($p < 0.001$). Despite the estimated declining incidence, given the aging US population, these investigators projected that the annual number of new cases will continue to rise with between 12,000 and 21,000 new IPF cases diagnosed annually by the year 2050. However, several limitations including the small total number of incident IPF cases (only 47 based on the broad case criteria) detract from the confidence that these results accurately reflect national trends.

In a second large-scale epidemiologic study, Raghu and colleagues [8] determined the annual incidence and prevalence of IPF in a 5% random sample of Medicare beneficiaries during the years 2001–2011. Using the ICD-9 codes 516.3 for IPF and 515 for post-inflammatory pulmonary fibrosis, the authors found the incidence of IPF to be stable over the time period at 93.7 cases per 100,000 person-years (95% CI = 91.9–95.4). However, it was notable that the annual cumulative prevalence increased dramatically from 202.2 cases per 100,000 persons in 2001 to 494.2 cases per 100,000 persons in 2011. To possibly account for the increasing cumulative prevalence in spite of the stable incidence rates, the investigators found that cases diagnosed in 2007 had longer survival times (4 years vs. 3.3 years) than those diagnosed earlier in the years that were evaluated. Because this study specifically examined patients 65 years or older (Medicare beneficiaries), a follow-up study by Raghu and colleagues [9] was performed to assess the incidence and prevalence in a younger population for comparison. A large patient claims database covering more than 89 million people aged 18–64 was examined, and it was found that the annual incidence decreased from 7.9 cases per 100,000 person-years in 2005 to 5.8 cases per 100,000 person-years in 2010. However, the cumulative prevalence was again found to have increased from 13.4 cases per 100,000 persons in 2005 to 18.2 cases per 100,000 persons in 2010.

Because of the concern that the use of electronic databases to determine incidence and prevalence of IPF may provide inaccurate data when case validation is not performed, Esposito and colleagues [10] developed algorithms using the HealthCore Integrated Research Database to identify IPF cases. Positive predictive values (PPVs) for their algorithms were determined after cases were adjudicated. Using a broad definition algorithm (an ICD-9 code-based algorithm similar to those used in prior studies), the PPV was found to be only 44.4%, suggesting that overes-

timation had occurred in prior studies. After correcting for the PPV of the algorithm, the authors determined the incidence of IPF to be 14.6 per 100,000 person-years with a prevalence of 58.7 per 100,000 persons.

Large-scale epidemiologic studies from the United Kingdom also suggest an increase in the incidence of IPF over time. Gribbin and colleagues [11] analyzed a large longitudinal general practice database in the United Kingdom from 1991 to 2003 and found that overall the incidence of IPF more than doubled during this time period. The overall crude incidence of IPF was 4.6 per 100,000 person-years, and the annual increase in the incidence of IPF was 11% (rate ratio 1.11; 95% CI = 1.09–1.13, $p < 0.0001$) after adjusting for sex, age, and geographic region. As in the studies described above, these investigators found the incidence of IPF was higher in men than women and increased with age (until >85 years of age). They could not determine if the trends observed were from increased case ascertainment due either to the expanding routine use of HRCT scanning or simply and increased awareness that perhaps emanated from globally visible consensus statements and multinational IPF drug trials.

Recently, Navaratnam and colleagues [12] extended the work of Gribbin and colleagues. Using the same longitudinal primary care database from the United Kingdom, these investigators determined the incidence of what they called the IPF clinical syndrome (IPF-CS) (defined by the diagnostic codes of idiopathic fibrosing alveolitis, Hamman-Rich syndrome, cryptogenic fibrosing alveolitis, diffuse pulmonary fibrosis, or idiopathic fibrosing alveolitis NOS but excluding connective tissue disease, extrinsic allergic alveolitis, asbestosis, pneumoconiosis, and sarcoidosis) from 2000 to 2008. The overall crude incidence of IPF-CS in their study was 7.44 per 100,000 person-years (nearly double the rate that Gribbin and colleagues reported for the prior decade); it was higher in men than women and generally increased with age. After adjusting for age, sex, and health authority, the incidence of IPF-CS increased by 5% annually from 2000 to 2008 (rate ratio 1.05, 95% CI = 1.03–1.06).

As highlighted in a recent systematic review by Hutchinson et al. [13], the majority of these data suggest the incidence of IPF is increasing worldwide. Because the disease is lethal within a relatively short period of time, mortality rates should mirror incidence rates, making mortality rate studies an additional, potentially rich source of data on these trends.

Mortality Rates and Secular Trends

Mortality rates for a condition are calculated as the number of deaths per year caused by the condition of interest, divided by the number of persons alive in the midyear population. Death certificate and census recording can provide data for such calculations. Because the validity of IPF death certificate data is largely unknown, studies using these data should be interpreted with caution. In the era of ICD-9 coding, when IPF (ICD-9 code 516.3) was coded on a death certificate, it was

generally accurate. However, because a significant proportion of decedents with IPF were coded as 515 (the code for post-inflammatory pulmonary fibrosis [PIPF]), IPF (whose ICD-9 code is 516.3) was typically under-recorded as the cause of death [14, 15]. In 1998 the ICD-10 coding system combined both IPF and PIPF into one diagnostic code (J84.1). Investigators have used this code in some studies (while making concerted efforts to exclude decedents with codes for known causes of ILD) in an attempt to capture a cohort most likely to have IPF. Other investigators have conducted similar studies and either intentionally or unintentionally included decedents with coexisting conditions associated with pulmonary fibrosis (e.g., connective tissue disease), leaving cohorts they labeled as having pulmonary fibrosis (PF) or IPF clinical syndrome (IPF-CS) [12, 16, 17]. Regardless of the term used, a great many decedents in these studies had IPF, and all of them almost certainly had progressive fibrotic lung disease that resulted in death.

In the first large-scale study of mortality rates from IPF, Johnston and colleagues examined ICD-9-coded death certificates from 1979 to 1988 and found that mortality rates from IPF (ICD-9 code 516.3) in England and Wales more than doubled over this time period [14]. Although more men than women died of IPF (60% of decedents) over the duration of the study period, mortality rates increased in both men and women (after standardization for age) and were greater among those of older age. Specifically, the mortality rate in those aged ≥75 years was eight times that of those aged 45–54. They identified higher mortality rates in the industrialized central areas of England and Wales, raising the possibility of occupational or environmental exposures as potential risk factors for the disease. Confirming and expanding the findings of Johnston and colleagues, Hubbard and colleagues examined ICD-9-coded death certificates and found that mortality rates from IPF rose in England, Wales, Scotland, Australia, and Canada from 1979 to 1992 [18].

Mannino and colleagues examined US death certificate data from 1979 to 1991 and found that age-adjusted mortality for pulmonary fibrosis (PF) increased 4.7% in men (from 48.6 deaths per million to 50.9 deaths per million) and 27.1% in women (from 21.4 deaths per million to 27.2 deaths per million). Again, PF-associated mortality increased with increasing age [16]. Higher mortality rates were identified in the West and Southeast, and lower mortality rates occurred in the Midwest and Northeast.

Using the same database as Mannino and colleagues, our group found that, from 1992 to 2003, PF-associated mortality rates increased 29.4% in men (from 49.7 deaths per million to 64.3 deaths per million) and increased 38.1% in women (from 42.3 deaths per million to 58.4 deaths per million) (Fig. 2.1). Mortality rates increased with advancing age and were consistently higher in men than in women; however, mortality rates increased at a faster pace in women than in men over this period of time [17].

Similar trends in mortality were recently reported in the United Kingdom; the overall age- and sex-adjusted mortality rate from IPF-CS from 2005 to 2008 was found to be 50.1 per million person-years. The overall annual increase in mortality was approximately 5% per year (RR = 1.05, 95% CI = 1.04–1.05) from 1968 to 2008, which equated to a sixfold increase in mortality over this study period [12].

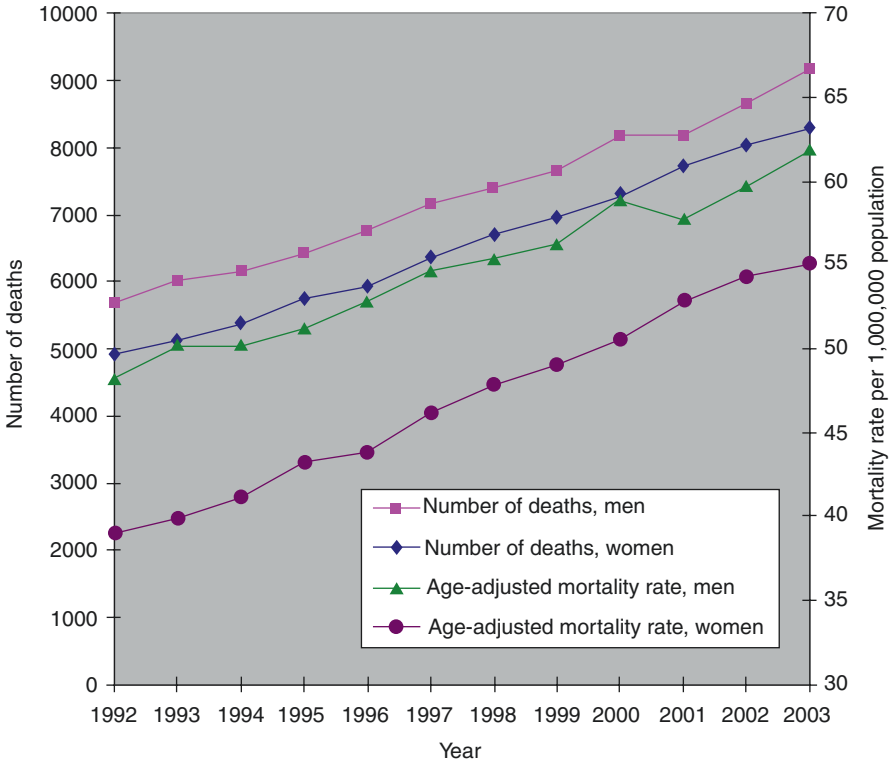

Fig. 2.1 Actual number of deaths per year (first y-axis) and age-adjusted mortality rates (second y-axis) in decedents with PF per 1,000,000 population from 1992 to 2003 in the United States. Mortality rates are standardized to the 2000 US Census Population. (Reprinted with permission of the American Thoracic Society. Copyright (C) 2012 American Thoracic Society. Olson et al. [17]. *Official journal of the American Thoracic Society*)

Hutchinson and colleagues also recently demonstrated a steadily increasing mortality rate in ten countries (including the United States and United Kingdom) using data collected between the years 1999 and 2012 [19]. These studies suggest mortality from IPF is increasing, and IPF is an important and growing public health concern, particularly in the aging population.

Risk Factors

Definitions and Limitations

Most studies of risk factors for IPF have been retrospective and subject to a number of limitations. Because the disease status and the exposure are assessed at the same time, a temporal relationship cannot be established. Furthermore,

systematic biases resulting from both exposure recall and diagnostic misclassification are possible. Recall bias exists when subjects recall past exposures differently than controls, and the net effect results in an exaggeration of risk [20]. Diagnostic misclassification bias arises when cases are incorrectly diagnosed with the disease or when controls have subclinical and undiagnosed disease. These scenarios have likely occurred in IPF, specifically in the time period before the routine use of HRCT scanning and the emergence of consensus statements on the classification of idiopathic interstitial pneumonias (IIPs) including IPF [1, 21]. The net effect of this type of error results in bias toward the null (a reduction in the strength of the association between exposure and disease). When identified, dose-response relationships strengthen the likelihood of a significant risk for the development of disease.

Genetic Risk Factors

Over the past decade, there have been many new and important studies evaluating genetic risk factors and susceptibility for IPF. These significant genetic risk factors are discussed separately in Chap. 8.

Cigarette Smoking

Cigarette smoking has been identified as a risk factor for IPF and for familial pulmonary fibrosis (FPF) in a number of case-control studies. In the United States, Baumgartner and colleagues performed an extensive analysis of the risk of IPF associated with smoking [22]. From 1989 to 1993, they compared 248 IPF patients at any of 16 referral centers to 491 controls matched for age, sex, and geography. They found that a history of ever smoking was associated with a 60% increase in risk for the development of IPF (OR = 1.6, 95% CI = 1.1–2.2). Additional analysis revealed that former smoking was associated with a 90% increased risk for the development of IPF (OR = 1.9, 95% CI = 1.3–2.9), whereas current smoking was not associated with an elevated risk (OR = 1.06, 95% CI = 0.6–1.8). A dose-response relationship was not identified; when compared to subjects with a less than 20 pack-year history, those who smoked 21–40 pack-years had an increased risk of IPF (OR = 2.26, 95% CI = 1.3–3.8), while those who smoked more than 40 pack-years did not (OR = 1.12, 95% CI = 0.7–1.9). However, among former smokers those who had recently stopped smoking possessed the highest risk for the development of IPF (for those who stopped smoking less than 2.5 years prior, OR = 3.5, 95% CI = 1.1–11.9; for those who stopped smoking 2.5–10 years prior, OR = 2.3, 95% CI = 1.3–4.2; for those who stopped smoking 10–25 years prior, OR = 1.9, 95% CI = 1.1–3.2; and for those who stopped smoking more than 25 years ago, OR = 1.3, 95% CI = 0.7–2.3). Similar to Baumgartner and colleagues, Miyake and colleagues compared 102 cases of IPF to 59 controls in Japan and found an increased risk of IPF only in those who smoked between 20 and 40 pack-years (OR = 3.23, 95% CI = 1.01–10.84) compared to never smokers [23].

Taskar and colleagues [24] conducted a meta-analysis that included the two investigations above [22, 23] plus three additional case-control studies from the United Kingdom [25, 26] and Japan [27]. Ever smoking was associated with a 58% increase in the risk for the development of IPF (OR = 1.58, 95% CI = 1.27–1.97). Given the high prevalence of smoking, these investigators determined that 49% of IPF cases could be prevented by entirely eliminating smoking within the population. The results from two other case-control studies from Mexico that were not included in the meta-analysis also suggest that smoking is a risk factor for IPF (OR adjusted = 3.2, 95% CI = 1.2–8.5 and OR adjusted = 2.5, 95% CI = 1.4–4.6) [28, 29]. An association between smoking and lung fibrosis has also been identified in FPF. Steele and colleagues compared 309 cases of FPF with 360 unaffected family members from 111 families and found that after adjustment for age and sex, ever smoking was associated with a greater than threefold increased odds of developing disease (OR = 3.6, 95% CI = 1.3–9.8) [30].

Occupational Exposures

Case-control studies have also found an association between a number of dusts and/or dusty environments and the development of IPF.

Metal Dusts

In a meta-analysis of five case-control studies published between 1990 and 2005, investigators found a significant association between metal dust exposure and the development of IPF (OR = 2.44, 95% CI = 1.74–3.40) [23–27, 31]. Baumgartner and colleagues identified a dose-response relationship between metal dust exposure and IPF. For subjects with less than 5 years of metal dust exposure, no association was identified (OR = 1.4, 95% CI = 0.4–4.9); however, for those with more than 5 years of metal dust exposure, the risk for the development of IPF was elevated more than twofold (OR = 2.2, 95% CI = 1.1–4.7) [31].

Hubbard and colleagues analyzed data from the pension fund archives of a metal engineering company and identified more deaths within this cohort than would be expected from national mortality data [32]. For all decedents with IPF and available records, an increased risk of IPF associated with metal dust exposure was not found. However, there was a dose-response relationship for those with more than 10 years of exposure as well as an increased risk of IPF (OR = 1.71, 95% CI = 1.09–2.68).

Pinheiro and colleagues analyzed mortality data from 1999 to 2003 and found an increased proportionate mortality ratio (PMR) and mortality odds ratio (MOR) among decedents with ICD-10 for pulmonary fibrosis and whose records also contained a code for “metal mining” (PMR = 2.4, 95% CI = 1.3–4.0; MOR 2.2, 95% CI = 1.1–4.4) and “fabricated structural metal products” (PMR = 1.9, 95% CI = 1.1–3.1; MOR 1.7, 95% CI = 1.0–3.1) [33]. In contrast a recent study from Sweden did not identify an association between metal dust exposure and IPF among patients on oxygen therapy (OR = 0.8, 95% CI = 0.43–1.44) [34].

Wood Dust

Results from two of five case-control studies (one from the United Kingdom and one from Japan) plus a meta-analysis of these studies suggest an association between wood dust exposure and IPF (summary OR= 1.94, 95% CI = 1.34–2.81) [23–26, 31, 35]. Discrepancies in results between individual studies may result from differences in the type of wood exposure. In a case-control study, investigators in Sweden found an association between both birch (OR = 2.4, 95% CI = 1.18–4.92) and hardwood dust (OR = 2.5, 95% CI = 1.06–5.89) exposure and IPF, but an association with fir dust (OR = 1.4, 95% CI = 0.82–2.52) was not identified [34].

Agriculture (Farming and Livestock)

Both farming and livestock exposures have been linked to an increased risk of IPF. In each of two case-control studies (one from the United States and one from Japan), investigators found a significant association between farming or residing in an agricultural region and IPF (summary OR = 1.65, 95% CI = 1.20–2.26) [24, 27, 31]. Exposure to agricultural chemicals was also associated with an increased risk of IPF in the Japanese study (OR = 3.32, 95% CI = 1.22–9.05) [27].

Results from two case-control studies (one from the United States and one from the United Kingdom) suggest an association between livestock and IPF (summary OR = 2.17, 95% CI = 1.28–3.68) [24, 25, 31]. In the US study, investigators observed a dose-response relationship between exposure to livestock and IPF; no association was identified for subjects with less than 5 years of exposure (OR = 2.1, 95% CI = 0.7–6.1), but subjects with more than 5 years of exposure to livestock had a greater than threefold increased risk for IPF (OR = 3.3, 95% CI = 1.3–8.3) [31].

Sand, Stone, and Silica

Results from a meta-analysis of four studies with contrasting results show a significant association between IPF and exposure to stone, sand, and silica dusts (summary OR = 1.97, 95% CI = 1.09–3.55) [23–25, 31, 35].

Miscellaneous Exposures

Baumgartner and colleagues found an association between IPF and hairdressing (OR = 4.4, 95% CI = 1.2–16.3) or raising birds (OR = 4.7, 95% CI = 4.7, 95% 1.6–14.1) after adjusting for age and cigarette smoking [31]. The latter association raises the possibility that some patients with chronic hypersensitivity pneumonitis might have been inadvertently diagnosed as having IPF. Residing in an urban or polluted area is another risk factor for IPF that had emerged from a case-control study in Japan (OR = 3.33, 95% CI = 1.26–8.79) [27], and a cluster of IPF cases was recently identified in dental personnel in Virginia, raising the possibility of occupational exposure in dental work as a potential risk [36].

The Natural History of IPF

Background

IPF has historically been described as a disease marked by inexorable progression [1, 2]. For patients with steadily progressive disease (i.e., moderately worsening lung function with each passing year), symptoms of breathlessness typically precede the diagnosis of IPF by 1–3 years [37–39], and median survival ranges from 2 to 3 years from the time of diagnosis [1, 2, 37–40]. However, careful inspection of results reveals significant heterogeneity in survival rates within cohorts [1, 41, 42]. Over the past few years, investigators have drilled deeply into their datasets in an attempt to better understand this heterogeneity. Although some of the heterogeneity may result from differences in disease severity at the time of diagnosis, it has become clear to the ILD field that there are actually different IPF phenotypes that can be defined by disease behavior over time (Fig. 2.2). For example, in every IPF study, a subgroup of long-term survivors is identified, a significant minority of IPF patients will suffer one or more acute exacerbations of IPF, and investigators are finding more and more patients with subclinical disease. What drives the phenotypic expression is unknown, but current theory

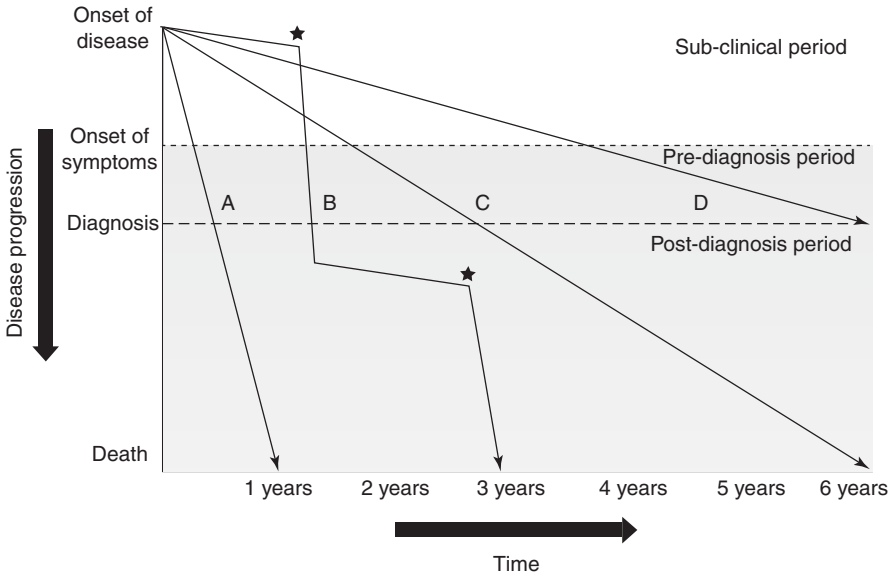

Fig. 2.2 Schematic representation of potential clinical courses of IPF. The y-axis represents disease progression from the onset of disease with a likely subclinical/asymptomatic period, which is followed by a period of symptoms that precede a formal diagnosis and then followed by the period of diagnosis through death with the x-axis representing time. As noted in the text, disease progression may be accelerated (A), relatively stable (C, D), or alternate between periods of relative stability marked by acute worsening (stars) (B). (Reprinted with permission of the American Thoracic Society. Copyright (C) 2012 American Thoracic Society. Ley et al. [43]. *Official journal of the American Thoracic Society*)

holds that it results from complex interactions involving the age and genetic makeup of the host and environmental exposures.

Predicting Survival

Nathan and colleagues examined data from their center collected over the previous decade and found that the median survival for 357 IPF patients was 45.9 months (3.8 years) from the time of their initial pulmonary function test. When stratified by disease severity, patients with percent predicted forced vital capacity (FVC%) ≥70%, 55–69%, or <55% had median survival values of 55.6 months (4.6 years), 38.7 months (3.2 years), and 27.4 months (2.3 years), respectively [42].

In addition to FVC, a number of other individual clinical, radiographic, physiologic, and pathologic variables as well as various biomarkers correlate with survival [43]. Several investigators have generated prognostic models that incorporate combinations of these variables collected at the time of diagnosis [38, 39]. For example, King and colleagues used data from 183 patients with biopsy-proven IPF and found that survival was dependent on a combination of age, smoking status, clubbing, extent of interstitial abnormalities, findings suggesting the presence of pulmonary hypertension on chest radiograph, total lung capacity (TLC), and abnormal gas exchange during maximal exercise [39]. Based on this model (with these clinical, radiological, and physiological [CRP] determinants), 5-year survival ranged from 89% in patients with lower scores to <1% in patients with higher CRP scores. Although this model and other similar modeling [44, 45] have revealed that differences in survival depend on baseline characteristics, none have been formally externally validated, and each model has limited ability to predict disease behavior in an individual patient.

Collard and colleagues determined that after adjustment for baseline values, 6- and 12-month change in any of a number of variables including dyspnea score, TLC, FVC, partial pressure of arterial oxygen, peripheral oxyhemoglobin saturation, and alveolar-arterial oxygen gradient predicted survival time [41]. As with baseline predictors, these seem to perform well at the group level [46, 47] but may not be predictive at the patient level. Furthermore, while these prediction models may provide some utility in mortality and respiratory hospitalization prediction, they perform very poorly in predicting risk of disease progression [48].

Rate of Decline in FVC

Data from the placebo arms of several therapeutic trials reveal that the annual decline in absolute FVC ranges from 0.15 to 0.22 L [49–56] (Table 2.3). Given the inclusion criteria (which typically seek to identify patients with earlier/milder disease) and exclusion criteria (which typically exclude patients with significant

comorbid conditions) used in these clinical trials [42], these estimates of disease progression as reflected by a decline in FVC are unlikely to apply to the general population of IPF patients.

The Underlying Cause of Death

The underlying cause of death (UCD) for the majority of patients with IPF is respiratory failure [16, 17, 43, 57]. Panos and colleagues reviewed a series of cases with mortality data published from 1964 to 1983 and found that among 326 deaths respiratory failure was the UCD in 38.7% of the decedents [57]. Using US death certificate data from 1979 to 1991, Mannino and colleagues found that in patients with pulmonary fibrosis, the UCD was the disease itself in 50% of decedents [16]. Our group extended the work of Mannino and colleagues by examining US death certificate data from 1992 to 2003 and found that pulmonary fibrosis was the UCD in 60% of

Table 2.3 Recent randomized, placebo-controlled trials in which the absolute decline in forced vital capacity (FVC) for the placebo group was reported over the study period [49–56]

Study	Drug	Baseline FVC, L (FVC%)	Absolute decline in FVC, L	Time of assessment	Annual rate of decline in FVC, L/year
ASCEND(King 2014) [106]	Pirfenidone	NR (68.6%)	−0.28/year	52 weeks	−0.28/year
INPULSIS-1 (Richeldi 2014) [107]	Nintedanib	2.85 (80.5%)	−0.24/year	52 weeks	−0.24/year
INPULSIS-2 (Richeldi 2014) [107]	Nintedanib	2.62 (78.1%)	−0.21/year	52 weeks	−0.21/year
TOMORROW (Richeldi 2011)	Nintedanib	2.70 (77.6%)	−0.19	52 weeks	−0.19/year
BUILD-3 (King 2011)	Bosentan	2.66 (73.1%)	−0.18	52 weeks	−0.18/year
Imatinib (Daniels 2010)	Imatinib	2.54 (65.5%)	−0.14	48 weeks	−0.15/year
Shionogi, (Taniguchi 2010)	Pirfenidone	2.47[a] (79.1%)[a]	−0.16[a]	52 weeks	−0.16/year[a]
Etanercept (Raghu 2008)	Etanercept	NR (63.0%)	−0.20	48 weeks	−0.22/year
Shionogi (Azuma 2005)	Pirfenidone	NR (78.4)[a]	−0.13[a]	36 weeks	−0.19/year[a]
IFIGENIA, (Demedts 2005)	NAC	2.36[a] (66.6%)[a]	−0.19[a]	52 weeks	−0.19/year[a]
GIPF-001 (Raghu 2004)	Interferon gamma-1b	NR (64.1%)	−0.16	48 weeks	−0.17/year

In those studies that were less than 52 weeks in duration, the annual rate of decline was determined from available data by assuming a constant rate of decline
Abbreviation: *NR* not reported
[a]Studies actually reported vital capacity (VC)

decedents with IPF [17]. Among IPF subjects in therapeutic trials, the UCD is a respiratory cause in nearly 80% [43, 51, 53, 58]. Taken together, these data reveal that over the past 50 years, the proportion of patients with IPF who are dying from (rather than with) the disease has grown, and these trends may reflect advances in diagnostic accuracy. However, another potential explanation is that effective therapies for some of the more common comorbid conditions (e.g., cardiovascular disease) result in patients being more likely to die from IPF rather than other treatable conditions (Table 2.4).

Apart from lung disease progression, UCDs in patients with IPF include coronary artery disease (CAD), pulmonary embolism, and lung cancer. While the proportion dying from cardiovascular disease has declined over time (see Table 2.4), patients with IPF appear to be at greater risk for CAD than patients with chronic obstructive pulmonary disease (COPD) (or other respiratory diseases requiring transplantation) [59–61] or matched people in the background population [62–64]. Thromboembolic disease and pulmonary embolism occur more often in patients with IPF than those with COPD and lung cancer or in people in the background population [63, 65, 66]. Furthermore, IPF decedents with a code for thromboembolic disease on their death certificates died younger (74.3 vs. 77.4 years in females [$p < 0.0001$] and 72.0 vs. 74.4 years in males [$p < 0.0001$]) than IPF decedents without codes for thromboembolic disease [65]. Compared with the background population, the risk for lung cancer is significantly elevated in patients with IPF, and this risk appears to be independent of smoking history [67, 68]; however, its overall effect on survival in this population remains unknown [69].

Phenotypic Subgroups

Long-Term Survivors

In studies conducted prior to the development of the current IIP classification system [16], nearly 30% of subjects with IPF were alive at 10 years from diagnosis

Table 2.4 The underlying cause of death in patients with idiopathic pulmonary fibrosis (see text) [16, 17, 57, 65]

Underlying cause of death / Study	Respiratory Pulmonary fibrosis	Respiratory Pneumonia	Respiratory COPD	Respiratory PE	Lung cancer	Cardio-vascular disease	Other
Panos (1964–1983)	39%	2.8%	NR	3.4%	10.4%	27.0%	14.1%
Mannino (1979–1991)	50.0%	NR	22.6%	NR	4.8%	22.6%	NR
Olson/ Sprunger [17] (1992–2003)/ (1998–2007) [65]	60.0%	2.4%	NR	1.74% [65]	2.9%	9.6%	23.4%

Abbreviation: *NR* not reported

[70, 71]. In retrospect it has been assumed that these long-term survivors had diseases other than IPF (e.g., non-specific interstitial pneumonia [NSIP]). However, using the ATS/ERJ criteria for the diagnosis of IPF [1] and cumulative data from the previous decade, Nathan and colleagues found that approximately one-quarter of their IPF patients (n = 357) survived more than 5 years from the time of diagnosis, and survival time was not necessarily associated with baseline FVC [42].

Rapid Progression from Diagnosis

Some patients with IPF follow a rapidly progressive clinical course from the onset (see Fig. 2.2). Selman and colleagues compared IPF patients with ≤6 months of symptoms (rapid progressors) to those with symptoms for ≥24 months (slow progressors) prior to first presentation. They found that despite the absence of differences between groups in baseline age, physiology, or gas exchange parameters, rapid progressors had a significantly increased risk of death when compared with slow progressors (HR = 9.0; 95% CI = 4.48–18.3) and were more likely to be male (OR = 6.5; 95% CI = 1.4–29.5) and either former or current smokers (OR = 3.04; 95% CI = 1.1–8.3) [72]. Additionally, the authors found a distinctive gene expression pattern in rapid progressors that was marked by overexpression of genes involved in morphogenesis, oxidative stress, and migration and proliferation of fibroblasts and smooth muscle cells.

Boon and colleagues examined gene expression profiles in surgical lung biopsy specimens and identified 134 transcripts that sufficiently distinguished relatively stable disease from progressive IPF [73]. They commented that similar to human cancers, genes related to cell proliferation, migration, invasion, and morphology were overrepresented in subjects with progressive disease. These findings highlight the heterogeneity of IPF at the transcriptional level and probably partly explain the varying clinical courses among patients with disease.

Stable Disease Followed by Accelerated Disease

Some IPF patients follow a relatively stable or mildly progressive course for months to years, and then their disease accelerates. Using data from the placebo arm of a large therapeutic trial, Martinez and his co-investigators observed that among patients who survived to the end of the 72-week study (78.6%), the mean FVC% decreased from 64.5 ± 11.1 to 61 ± 14.1, the mean DLCO% decreased from 37.8 ± 11.1% to 37.0 ± 19.9%, and there was little worsening in dyspnea [58]. However, among 36 subjects who died (21.4%), death was IPF-related in 32 patients (89%) and the result of disease progression in 20 patients (56%). Of those deaths resulting from progressive IPF, 47% were acute (deterioration over 4 weeks or less), and 50% were subacute (progression over weeks to months), thus demonstrating that disease progression accelerates prior to death in some patients.

Acute Exacerbations of IPF

In Japan it has been recognized for over 30 years that some patients with IPF experience acute respiratory decline [74, 75], but this was thought to be a rare phenomenon in Western countries until recently [76]. However, sudden respiratory decline in a previously stable patient is now a well-recognized phenomenon that can affect IPF patients around the world. When these events appear to be idiopathic, they have been termed acute exacerbations (AEx) of IPF and are associated with significant morbidity and mortality [77].

To help unify research efforts, Collard and colleagues proposed the following definition for AEx: (1) a previous or concurrent diagnosis of IPF, (2) unexplained development of dyspnea or worsening within 30 days, (3) high-resolution computed tomography (HRCT) with new bilateral ground-glass abnormality and/or consolidation superimposed on a background pattern consistent with IPF, (4) no evidence of pulmonary infection by endotracheal aspirate or bronchoalveolar lavage (BAL), and (5) exclusion of alternative causes including left heart failure, pulmonary embolism, and identifiable causes of acute lung injury [77].

Since these criteria were proposed, two retrospective analyses have better defined the incidence of risk factors for AEx and mortality from these events. Kondoh and colleagues retrospectively studied 74 patients with IPF and observed that the 1-year, 2-year, and 3-year incidence of AEx was 8.6% (95% CI = 1.7–12.6%), 12.6% (95% CI = 4.5–20.0%), and 23.9% (95% CI = 12.9–33.5%), respectively [78]. In a multivariate analysis, they found that a decline of 10% in FVC at 6 months, a higher BMI, and greater dyspnea at baseline were significant risk factors for AEx. The survival time in subjects with an AEx was significantly shorter (median 26.4 months) compared to those without an AEx (median 52.8 months). Song and colleagues reviewed records of 461 patients with IPF with a median follow-up time of 22.9 months and observed that 96 patients (20.8%) had either a definite (using Collard's criteria) or suspected AEx [79] and 17 of these patients (17.7%) experienced multiple episodes of AEx. The 1-, 2-, and 3-year incidences (excluding patients who presented concurrently with a new diagnosis of IPF while having an AEx event) were 11.6%, 16.3%, and 18.2%, respectively. A multivariate analysis showed that a lower FVC% and never smoking were significant risk factors for an AEx, and AEx events were associated with poor outcomes: 50% of patients died during hospitalization for the AEx, 90% of those who required mechanical ventilation died, and 60% of patients died within 90 days. For those who lived past 90 days, the median survival was 15.5 months as compared with 60.6 months for those without an AEx ($p < 0.001$). Clearly, AEx are not as rare as once believed and are associated with poor survival.

Additional data from recent prospective therapeutic trials have reported AEx frequencies ranging from 1.7% over 96 weeks to 14.2% over 36 weeks [49–52, 54, 56, 58, 80–83] (Table 2.5). Differences in baseline patient populations, diagnostic criteria used, and case-finding methods likely account for some of the variability in reported frequency of AEx. These discordant data confirm that additional research regarding AEx of IPF is needed.

Table 2.5 Recent randomized, placebo-controlled trials in which the incidence or percentage of patients with acute decompensation and/or an acute exacerbation was reported [49–52, 54, 58, 80–83]. Definitions from the study for acute exacerbation, acute worsening, or acute decompensation are given below

Study	Drug	Placebo cohort (*n*)	FVC (L or % predicted)	Definition	Incidence or percentage reported	Study period
IMPULSIS-1 (Richeldi 2014) [107]	Nintedanib	204	2.85 (80.5%)	Acute exacerbation[a]	5.4%	52 weeks
IMPULSIS-2 (Richeldi 2014) [107]	Nintedanib	219	2.62 (78.1%)	Acute exacerbation[a]	9.6%	52 weeks
ACE-IPF (IPFnet 2012)	Warfarin	73	58.7%	Acute exacerbation[a]	2.7%	28 weeks (mean follow-up)
TOMORROW (Richeldi 2011)	Nintedanib	87	2.70 L	Acute exacerbation[b]	15.7 per 100 patient-years	52 weeks
BUILD-3 (King 2011)	Bosentan	209	2.66 L	Acute exacerbation[c]	2.9%	80 weeks (mean study duration)
STEP-IPF (IPFnet 2010)	Sildenafil	91	58.7%	Acute exacerbation[d]	4.4%	12 weeks
STEP-IPF (IPFnet 2010)	Sildenafil	91	58.7%	Acute exacerbation[d]	7.7%	24 weeks (last 12 weeks on therapy)
Imatinib (Daniels 2010)	Imatinib	60	2.54 L	Acute worsening[e]	1.7%	96 weeks
Shionogi (Taniguchi 2010)	Pirfenidone	104	2.47 L	Acute exacerbation[f]	3.8%	52 weeks
INSPIRE (King 2009)	INF-γ	275	73.1%	Acute decompensation[g]	8.7%	77 weeks (mean study duration)
INSPIRE (King 2009)	INF-γ	275	73.1%	Acute exacerbation[g]	5.4%	77 weeks (mean study duration)
BUILD-1 (King 2008)	Bosentan	83	69.5%	Acute decompensation[h]	3.6%	54 weeks (mean study duration)

(continued)

Table 2.5 (continued)

Study	Drug	Placebo cohort (*n*)	FVC (L or % predicted)	Definition	Incidence or percentage reported	Study period
Shionogi, (Azuma 2005)	Pirfenidone	35	78.4%	Acute exacerbation[i]	14.2%	36 weeks
GIPF-001, (Raghu 2004; Martinez 2005)	Interferon gamma-1b	168	64.1%	Death from either progression of IPF or acute respiratory distress syndrome after a period of decompensation lasting <4 weeks	4.8%	76 weeks (median observation period)

[a]Acute exacerbation was determined via adjudication as part of the study

[b]Acute exacerbation definition: Progression of dyspnea over several days to 4 weeks, new parenchymal ground-glass abnormalities on x-ray or HRCT, and a decrease in $PaO_2 \geq 10$ mmHg or increase in alveolar-arterial oxygen gradient, within a 1-month period that could not be otherwise explained

[c]Acute exacerbation definition: Unexplained rapid deterioration of condition within 4 weeks with increasing dyspnea requiring hospitalization and O_2 supplementation

[d]Acute exacerbation definition: (1) Unexplained worsening of dyspnea or cough within 30 days, triggering medical care with no clinical suspicion or overt evidence of cardiac event, pulmonary embolism, deep venous thrombosis to explain worsening of dyspnea, or pneumothorax; (2) one of the following radiologic or physiologic findings: (a) new ground-glass opacity or consolidation on CT scan or new alveolar opacities on chest x-ray or (b) decline of ≥5% in resting room air SpO_2 from last recorded level or decline of ≥8 mmHg in resting room air PaO_2 from last recorded level; and (3) no clinical or microbiologic evidence of infection

[e]Acute worsening was not otherwise specified

[f]Acute exacerbation definition: Worsening clinical features within 1 month including progression of dyspnea, new radiographic/HRCT ground-glass abnormalities without pneumothorax or pleural effusion, a decrease in PaO_2 by 10 mmHg or more, and exclusion of obvious causes including infection, cancer, pulmonary thromboembolism, malignancy, or congestive heart failure

[g]Acute respiratory decompensation: Evidence of all of the following must be present within a 4-week period: worsening PaO_2 or new or significant increase in the use of supplemental oxygen, clinically significant worsening of dyspnea, and new or worsening radiographic abnormalities on chest radiograph or HRCT. Acute exacerbation = Evidence of all of the following must be present within a 4-week period: worsening PaO_2 at rest (≥8 mmHg drop from most recent pre-worsening value), clinically significant worsening of dyspnea, new ground-glass opacities on HRCT, and all other causes, such as cardiac, thromboembolic, aspiration, or infectious processes, have been excluded

[h]Acute decompensation definition: Unexplained rapid deterioration over 4 weeks with increased dyspnea requiring hospitalization and oxygen supplementations of ≥5 L/min to maintain a resting oxygen saturation by blood gas of ≥90% or $PaO_2 \geq 55$ mmHg (sea level) or $PaO_2 \geq 50$ mmHg (above 1400 m)

[i]Acute exacerbation definition: Worsening clinical features within 1 month with progression of dyspnea over a few days to less than 5 weeks, new radiographic/HRCT parenchymal abnormalities without pneumothorax or pleural effusion, a decrease in PaO_2 by 10 mmHg or more, and exclusion of apparent infection by absence of *Aspergillus* and pneumococcus antibodies in blood, urine for *Legionella pneumophilia*, and sputum cultures

Subclinical Disease

Based largely on studies of family members of patients with familial FPF, it is apparent that asymptomatic/subclinical disease precedes the development of symptomatic IPF. Some asymptomatic relatives from FPF kindreds have evidence of alveolar inflammation on bronchoalveolar lavage [84] or evidence of pulmonary fibrosis (with a usual interstitial pneumonia [UIP] pattern of injury) on either imaging or on the basis of a surgical lung biopsy [30, 85].

Among 417 unaffected (by self-report) family members from 111 families with FPF, 28 (6.7%) had possible disease (based on chest radiographs), and 33 persons (7.9%) had either probable (based on HRCT abnormalities) or definite (based on either surgical lung biopsy or autopsy evidence of an IIP) disease [30]. Rosas and colleagues evaluated 143 asymptomatic subjects from 18 kindreds with FPF and found that 31 subjects (22%) had HRCT changes (including increased septal lines, peribronchovascular thickening, reticulation, and ground-glass opacities) consistent with interstitial lung disease (ILD) [85]. When compared with affected family members, those with HRCT evidence of ILD but without symptoms were younger (46 years vs. 67 years, $p < 0.001$). These findings suggest that progression of asymptomatic to symptomatic disease may occur over a period of decades; however, the proportion of people who will progress, over what time frame progression occurs, and which variables predict progression remain unknown.

In 1982 Bitterman and colleagues assessed 17 clinically unaffected family members of three families with FPF and found that 8 (47%) had evidence of alveolar inflammation on BAL studies [84]. Two of these patients were reassessed 27 years later; one had developed symptomatic IPF, and the other was asymptomatic but did have evidence of early IPF on HRCT, suggesting that there may be a latency period of two to three decades in some cases from early asymptomatic alveolar inflammation to overt fibrotic disease [86].

Additional evidence suggesting that subclinical disease precedes symptomatic clinical disease is found in reports of acute exacerbations in the subclinical period. Case reports and series have described patients without known ILD who present with acute respiratory failure (clinical adult respiratory distress syndrome [ARDS]) and histopathologic findings of diffuse alveolar damage (DAD) superimposed on a UIP pattern, which is the same pattern observed in AEx of IPF [79, 87–89].

Patients with subclinical IPF and lung cancer who undergo surgical lobectomy appear to be at an increased risk of AEx. In a review of 1148 patients with lung cancer who underwent thoracotomy, investigators found 15 patients who developed postoperative ARDS. Eleven (73%) of these patients had both interstitial abnormalities on preoperative CT and a UIP pattern in resected lung tissue. The risk of postoperative ARDS was significantly higher in those with evidence of subclinical IPF on CT imaging (8.8%) compared to those without ILD (0.4%) ($p < 0.001$) [90]. Fukushima and colleagues found subpleural fibrosis in 127 of 776 patients (16.4%) who underwent lobectomy for lung cancer. Three patients progressed acutely following surgery, and another seven progressed to classic IPF over a period of 5 years [91].

Araya and colleagues reviewed 14 autopsy cases of idiopathic DAD (acute interstitial pneumonia [AIP]) and found that 50% of cases also had evidence of subpleural fibrosis, suggesting that some cases of AIP may in fact be the result of an AEx of subclinical IPF [92].

With the increasing use of HRCT, a new category of subclinical ILD has been defined. Interstitial lung abnormalities (ILAs) have recently been investigated in a number of large cohort studies [93, 94]. In the Framingham Heart Study and the AGES-Reykjavik study, it was determined that 7% of participants had ILAs present on CT imaging. Furthermore, in the COPDGene study, ILAs were present in 8% of participants, whereas 9% of participants in the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study had ILAs present. Using these cohorts Putman and colleagues demonstrated that ILAs were associated with greater all-cause mortality, and in the AGES-Reykjavik cohort, ILAs were associated with greater mortality due to pulmonary fibrosis [94]. Notably, ILAs were associated with the MUC5B promoter polymorphism that has been associated with IPF [93]. Given the commonality of ILAs in these cohorts, it is clear that they do not universally lead to the development of IPF. However, it is possible that some ILAs may represent an early stage of disease, and detection could allow for early treatment.

Although subclinical disease is becoming increasingly recognized [95], many questions concerning the clinical significance of subclinical disease remain. Longitudinal studies are needed to determine risk factors for disease progression, the time period over which the transition from subclinical to clinically relevant disease occurs, and whether early interventions can improve outcomes.

Specific Clinical Phenotypes of Disease

Identifying specific clinical phenotypes of disease is paramount, because doing so may provide insight into the pathobiology of disease [96]. Patients with IPF and either disproportionate pulmonary hypertension or concurrent emphysema are believed by some experts to represent distinct clinical phenotypes of disease, and investigation of these concurrent processes has furthered our understanding of the heterogeneous clinical course.

IPF with Pulmonary Hypertension

The development of pulmonary hypertension in patients with IPF was once believed to be due to vascular obliteration from pulmonary fibrosis. However, in several studies investigators have not found a clear association between the severity of fibrosis and the presence or severity of pulmonary hypertension, suggesting that additional factors are involved [97–99]. Regardless of the underlying mechanisms that lead to the development of pulmonary hypertension, its presence negatively impacts survival [39, 98, 100, 101].

Combined Pulmonary Fibrosis and Emphysema

There is increasing recognition of the coexistence of pulmonary fibrosis and emphysema (a syndrome termed combined pulmonary fibrosis and emphysema [CPFE]) within individual patients. CPFE is characterized by relatively preserved static and forced lung volumes, a disproportionately reduced diffusing capacity, and a high prevalence of pulmonary hypertension [102, 103]. In patients with apparent IPF, concurrent evidence of emphysema on HRCT imaging ranges from 18.8% to 50.9%, and the median survival in such patients is estimated at 2.1–8.5 years [104]. It remains unclear if patients with CPFE have a worse survival compared to those with IPF alone. Mejía and colleagues suggested that the reduced survival among subjects with CPFE compared to IPF subjects was due to the presence of pulmonary hypertension in patients with CPFE [105].

Summary

Over the past two decades, results from multiple studies have advanced our understanding of the natural history of IPF. It has become evident that IPF, once thought to be a steadily progressive disease in all patients, may actually follow any number of different courses. This heterogeneity makes it impossible to confidently determine how the disease will behave over time in an individual patient. However, given this knowledge investigators may now embark on studies to explain this variability and tease out the pathobiologic mechanisms that drive it. Epidemiologic studies suggest that IPF should no longer be considered an orphan disease, especially considering that mortality rates are similar to those associated with some common malignancies. Case-control studies have revealed potential exposures for disease development, but these studies are subject to a number of potential biases. Maintaining the momentum of clinical research and propelling the field forward will require carefully planned, well-designed studies to further decipher disease heterogeneity, identify additional risk factor for disease development, and determine how to prevent and treat this devastating disease.

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