Risk factors for idiopathic pulmonary fibrosis

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Key words
- Idiopathic pulmonary fibrosis
- Pulmonary fibrosis
- Smoking
- Environmental exposure
- Gastroesophageal reflux
- Risk factors

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Idiopathic pulmonary fibrosis (IPF) represents a specific disease of chronic progressive interstitial pneumonia, of unknown etiology, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of UIP[1].

It is the most common idiopathic interstitial pneumonia, with a mean survival of 3-5 years[2,3]. It is 3 to 5 times most common in older than 75 years-old as compared to less than 55 years old persons. The disease is rare in people than 55 years old, and is most common in male.

Its **pathogenesis** is in most aspects unknown, however, great advances have been made last years[4,5]. The treatment of IPF remains unsuccessful, although recently the first drug has been approved for the treatment of mild to moderate disease[5], and the promising role of stem cell application is explored[6,7].

The definition of IPF requires the exclusion of other forms of interstitial pneumonia including other idiopathic interstitial pneumonias and ILD associated with environmental exposure, medication, or systemic disease[1,12].

Although IPF is by definition of unknown etiology, there are certain known risk factors (Table 1).

Environmental exposure is considered as risk factor. Patients with IPF have more common occupational exposure to metal dust, (brass, lead, and steel) and wood dust (pine). Farming, raising birds, hair dressing, stone cutting/polishing, and exposure to livestock and to vegetable dust/animal dust have also been associated with IPF[8-12]. In a meta-analysis of six case-controlled studies IPF was found to be associated with six risk factors including (summary odds ratios [95% confidence intervals]), smoking (1.58 [1.27-1.97]), farming (1.65 [1.20-2.26]), livestock (2.17 [1.28-3.68]), wood dust exposure (1.94 [1.34-2.81]), metal dust (2.44 [1.74-3.40]), and stone/sand work (1.97 [1.09-3.55]).[8] Despite the limitations of these studies not allowing to an etiologic correlation, there are concern if IPF is a really idiopathic or of known etiology from environmental or occupational factors[8,9].

A history of **smoking** is associated with an increased risk for the development of IPF. More than 70% of IPF patients are smokers or ex-smokers. Smoking increases the risk by 1.5 to 2.5 times. The risk is higher in smokers of >20 pack-years. Survival is higher in non smokers than in ex-smokers or ex-smokers and smokers as a group[13,14]. Recently increased attention has been given to the, so-called, **combined pulmonary fibrosis emphysema syndrome**[15].

Several studies have investigated the possible role of **chronic viral**

TABLE 1. Risk factors for idiopathic pulmonary fibrosis.

Factor	Increased risk	Comments
AGE	3 to 5 times more common in individuals of more than 75 years-old as compared to people less than 55 years-old.	Difficult the detection of the exact begging of the disease. Younger people have more severe disease.
SMOKING	70% of the patients are smokers or ex-smokers. Smoking increases the risk by 1.5 - 2.5 times. Risk in smokers of >20 pack-years.	Increased risk in both sporadic and familial IPF.
SEX	male: female = 60/40	Male have increased risk in all age groups. Survival is higher in female.
Environmental Exposure		
Metal dust	Risk 2- 3 times higher.	Requires many years of exposure. Main metals steal, brass and lead.
Wood dust	Risk 2- 3 times higher.	Requires many years of exposure.
Stone dust or sand	Risk 1.5-2.5 3 times higher.	Exposure to fine particles of sand may cause silicosis.
Farming, livestock, hair dressing, stone cutting/polish	Correlation with higher risk	
Viral agents		
Epstein-Barr virus (EBV), cytomegalovirus (CMV), human herpes virus (HHV)-7, and HHV-8, antibodies against hepatitis C (HBV)	Definite conclusions about the role of infection in IPF does not exist.	May develop other forms of interstitial pneumonias.
Gastroesophageal reflux (GER)	GER is common in IPF.	Clinically silent in many. Alkaline GER is common.
Familial history	2–5% of I PF patients may develop familial IPF	Tends to be more prevalent in younger ages, to be more aggressive and to exist many years before the symptoms. Correlation with *surfactant protein C, human telomerase reverse transcriptase (hTERT), human telomerase RNA (hTR).* Genetic testing is not recommended.

infection in the etiology of IPF, including Epstein-Barr virus[16-22], cytomegalovirus, (CMV)[23], human herpes virus (HHV)-7[24], and HHV-8[25], and serum antibodies for hepatitis C (HBV)[26,27].

An increasing body of evidence has provided useful insights about a potential link between diffuse lung fibrosis and **gastroesophageal reflux (GER)** through its presumed association with microaspiration. A high prevalence of abnormal acid gastro-esophageal reflux (identified by 24-h pH monitoring) in patients with IPF—almost 90%—was first reported in two different cohorts[29-32]. However, a much smaller proportion of patients complain of heartburn-related symptoms, making the diagnosis of abnormal acid GER clinically occult and thus insidious. Several reports have associated anti-reflux treatment with improved survival and substantial functional and radiological benefits in patients with IPF[30-32].

Diabetes mellitus may also be a risk factor for IPF[33].

Familial history is correlated with IPF[33,34]. About 2-5% of the patients may present with familial forms of IPF (defined as affecting two or more members of the same primary biological family), which may reappear after the next generation. Familial IPF is developed in younger people, may be more aggressive, and to exists many years before symptoms. Is correlated with surfactant protein C, human telomerase reverse transcriptase (hTERT), and human telomerase RNA (hTR). The evidence-based committee does not recommend genetic testing in patients with either familial or sporadic IPF as part of clinical evaluation

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