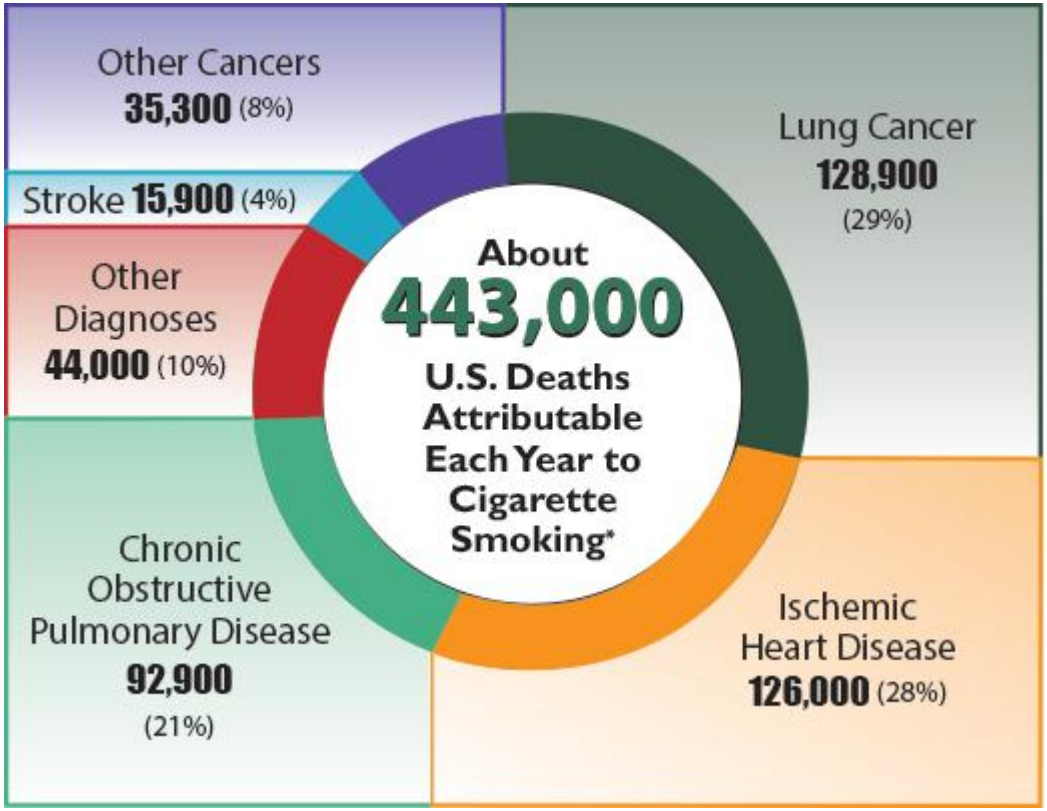
Epidemiology and classification of smoking related interstitial lung diseases

Šterclová M.
Department of Respiratory Diseases, Thomayer Hospital, Prague, Czech Republic

Supported by an IGA Grant No G 1207 (NT13433-4/2012).

Risk of cigarette smoking



-Tobacco kills up to half of its users.
-Tobacco kills nearly 6 million people each year.
-Five million of those deaths - direct tobacco use.
-More than 600 000 - second-hand smoke.
- Nearly 80% of the world's one billion smokers live in low- and middle-income countries.

http://www.who.int/mediacentre/factsheets/fs339/en/

http://www.cdc.gov/tobacco/data_statistics/tables/health/attrdeaths/index.htm

Second hand smoke

- More than 4000 chemicals in tobacco smoke, 250 harmful, 50 cause cancer
- No safe level of exposure to second-hand tobacco smoke.
- Almost half of children regularly breathe air polluted by tobacco smoke in public places
- Over 40% of children have at least one smoking parent
- 600 000 premature deaths per year
- In 2004, children accounted for 28% of the deaths attributable to second-hand smoke

Smoking related interstitial lung diseases

Major ILDs of known aetiology (~35% of all patients with ILDs)	
	Pneumoconioses (e.g. asbestosis, silicosis)
	Extrinsic allergic alveolitis (hypersensitivity pneumonitis)
	Iatrogenic ILD caused by drugs and/or radiation
	Post-infectious ILD
Major ILDs of unknown aetiology (~65% of all patients with ILDs)	
	Sarcoidosis
	Idiopathic interstitial pneumonias, of which the most important are:
	IPF with a histopathological pattern of usual interstitial pneumonia (~55% of IIPs)
	Nonspecific interstitial pneumonia (~25% of IIPs)
	Respiratory bronchiolitis ILD, occurring in smokers (~10% of IIPs)
	Desquamative interstitial pneumonia (~5% of IIPs)
	Cryptogenic organising pneumonia (~3% of IIPs)
	Lymphoid interstitial pneumonia (~1% of IIPs)
	Acute interstitial pneumonia (~1% of IIPs)
	ILD in CTDs and in collagen-vascular diseases, of which the most important are:
	ILD in rheumatoid arthritis
	ILD in progressive systemic sclerosis

Smoking related interstitial lung diseases- less than 1 in 2000

- **Vasculitides**
- **Granulomatosis with polyangiitis (Wegener's)**
- **Microscopic polyangiitis**
- **Eosinophilic granulomatosis with polyangiitis (Churg–Strauss)**
- **Behçet's disease**
- **Takayasu's arteritis**
- **Autoimmune diseases**
- **Anti-basement membrane syndrome**
- **Pulmonary alveolar proteinosis**
- **Disorders of genetic origin**
- **Lymphangioleiomyomatosis associated with tuberous sclerosis**
- **Multiple cystic lung disease in Birt–Hogg–Dubé syndrome**
- **Primary ciliary dyskinesia**
- **Other idiopathic disorders (lung limited)**

Smoking related interstitial lung diseases- less than 1 in 2000

- **Idiopathic eosinophilic pneumonias**
- **Tracheobronchopathia osteochondroplastica**
- **Tracheobronchomegaly (Mounier–Kuhn syndrome)**
- **Idiopathic bronchiolitis**
- **Other rare diseases**
- **Thoracic endometriosis**
- **Langerhans' cell histiocytosis**

Smoking related interstitial lung diseases

- CS causative: RB-ILD
  DIP
  PLCH
  AEP
  SRIF

- CS modifying: IPF
  Inhalation exposure to organic/anorganic antigens
  CTD-ILD
  CPFE
  Goodpasture syndrome

Epidemiology of RB-ILD

TABLE 3 Demographic and clinical characteristics of 692 subjects according to the presence of thin-section computed tomography patterns

	RB-like pattern	OCIP- and UIP-like patterns	Indeterminate pattern	Normal	p-value#
Subjects n	109	28	21	534	
Age yrs	55.5±5.4	60.3±6.5	58.1±7.1	57.2±5.9	0.001
Sex					
Female	36 (33.0)	4 (14.3)	4 (19.1)	185 (34.6)	
Male	73 (67.0)	24 (85.7)	17 (81.0)	349 (65.4)	0.070
Smoking status					
Former	11 (10.1)	5 (18.5)	3 (14.3)	159 (29.8)	
Current	98 (89.9)	22 (81.5)	18 (85.7)	375 (70.2)	<0.001
Number of cigarettes per day					
<20	24 (22.0)	8 (28.6)	5 (23.8)	122 (22.9)	
20	46 (42.2)	7 (25.0)	10 (47.6)	230 (43.1)	
>20	39 (35.8)	13 (46.4)	6 (28.6)	182 (34.1)	0.633
Number of smoking yrs					
<35	29 (26.6)	5 (17.9)	5 (23.8)	183 (34.3)	
35–39	32 (29.4)	8 (28.3)	6 (28.6)	125 (23.4)	
⩾40	48 (44.0)	15 (53.6)	10 (47.6)	226 (42.3)	0.343
Yrs of stopping smoking	3.8±3.1	3.8±3.3	3.5±2.1	5.2±3.3	0.438
FEV_1 % pred	93.0±18.8	89.0±17.3	98.0±18.7	95.3±20.6	0.317
FVC % pred	101.4±21.0	100.8±18.4	106.9±18.7	103.8±21.4	0.574

Data are presented as mean±SD or n (%), unless otherwise stated. RB: respiratory bronchiolitis; OCIP: other chronic interstitial pneumonia; UIP: usual interstitial pneumonia; FEV_1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity. #: derived from Fisher's exact test for categorical variables and ANOVA analysis for continuous variables.

Sverzellati N, et al. Eur Respir J 2011; 38: 392-400.

Epidemiology of DIP

TABLE 1 Epidemiological and clinical features of desquamative interstitial pneumonia

	Liebow [1]	Tubbs [3]	Yousem [5]	Ryu [6]	Total
Cases n	18	26	36	23	103
Males/females n	10/8	17/9	26/10	11/12	64/39
Age at onset years median (interquartile range)	45 (16–63)	51 (24–75)	42 (17–67)	46 (26–69)	46 (16–75)
Smoking history	NS	15/26 (58)	30/33 (91)	20/23 (87)	65/82 (79)
Mean smoking exposure pack-years (95% CI)		⩾10	36 (10–71)	31 (10–90)	
Occupational history, cases exposed	1 exposed to plastic fumes and dusts 2 exposed to hairsprays	NS	NS	No environmental exposure or underlying disease identified	
Symptoms					
Dyspnoea	18/18 (100)	23/26 (88.5)	29/34 (85)	20/23 (87)	90/101 (89)
Cough	14/16 (87.5)	18/26 (75)	26/32 (81)	10/23 (43)	68/97 (70)
Sputum	4/16 (25)	NS	17/33 (52)	NS	21/49 (43)
Weight loss	6/10 (60)	1/26 (4)	NS	NS	7/36 (20)
Chest pain	9/12 (75)	1/26 (4)	NS	4/23 (17)	14/61 (23)
Haemoptysis	1/18 (5.5)	2/26 (8)	NS	NS	3/44 (7)
Asymptomatic	0/18 (0)	1/26 (4)	5/34 (15)	1/23 (4)	7/101 (7)
Physical signs					
Cyanosis	7/10 (70)	3/26 (11.5)	NS	NS	10/36 (28)
Crackles	<50%	17/26 (65)	5/9 (56)	13/23 (57)	35/58 (60)
Clubbing	5/9 (55.5)#	12/26 (46)	15/36 (42)#	6/23 (26)	38/94 (40)

Data are presented as n/N (%), unless otherwise stated. NS: not specified. #: clubbing sometimes disappeared after steroid therapy.

Godbert J, et al. Eur Respir Rev 2013; 128:117-123.

Epidemiology of PLCH

Table 1 Contrasting pediatric and adult PLCH

	Pediatric PLCH	Adult PLCH
Demographic features		
Peak age at presentation	1-3 yrs [16]	20-40 yrs [5]
Smoking history	Infrequently described [16,17]	Reported in > 95% [5,12]
Imaging findings; chest CT		
Distribution of abnormalities	Frequently involves lower lobes [18]	Sparing of bases and costo- phrenic angles is typical [19-21]
Biological character		
Clonality	Invariably reported [22-24]	Suspect reactive rather than clonal [25]
Clinical Presentation		
Single system vs multi-system presentation	Typically part of multi-system LCH [16]	Single system disease in > 80% of patients [5]
Management		
Pharmacotherapy with prednisone/ vinblastine	Complete or partial response frequently observed [26,27]	Insufficient data available; likely limited response
Smoking cessation	Limited role as tobacco exposure not involved in most cases	Main and first line therapy in all adult smokers [28,29]

-Incidence of LCH is 4-9 cases per million/year in children
-Prevalence PLCH in 4-5% of all diffuse lung disease

Suri LS, et al. Orphanet J Rare Dis 2012;7:16.

Epidemiology of AEP

- Incidence 9,1 per 100 000 p/year
- Recent initiation of tobacco smoking, increase quantity of smoked cigarettes, rechallenge with reccurence
- Second hand smoke (massive), flavoured cigars, World Trade Center dust (large particle sized silicate, fly ash, asbestos fibres)

Epidemiology of SRIF

- SRIF - chronic interstitial fibrosis common in cigarette smokers
- Uniform thickening of alveolar septa by collagen deposition with minimal associated inflammation
- Lobectomy specimens from smokers - SRIF in 45% (9/20 cases), mean age 65 (52-81)
- 50 % current and 50 % ex-smokers, mean pack years 39 and 38
- No specific pulmonary function abnormalities, no specific radiographic findings
- No evidence of progressive interstitial lung disease (mean 16 months follow up)

Katzenstein AL, et al. Modern Pathology 2012; S1: S68-78.

Epidemiology of SRIF

- SRIF masked by or included among other smoking-related disorders
- COPD, CPFE, DIP, fibrosing NSIP, UIP
- CT findings - 2563 smokers, GGO and reticular opacities in 2.2% (Lederer)
- Washko - interstitial abnormalities on HRCT in 8% of 2416 smokers

Epidemiology of SRIF

TABLE 4 Interstitial lung disease for selected characteristics by computed tomography patterns

	RB-like pattern	OCIP- and UIP-like patterns	p Heterogeneity
Age (10 yrs)	0.51 (0.32–0.84)	2.06 (0.94–4.51)	0.002
Sex			
Female	1	1	
Male	1.12 (0.70–1.77)	2.71 (0.90–8.15)	0.136
Smoking status			
Former smokers	1	1	
Current smokers	3.35 (1.70–6.58)	2.29 (0.80–6.60)	0.545
Number of cigarettes·day^{-1} (10 units)	1.10 (0.89–1.37)	1.18 (0.81–1.73)	0.734
Number of smoking yrs (10 yrs)	1.36 (0.91–2.04)	1.17 (0.60–2.26)	0.687

Data are presented as odds ratio (95% confidence interval), estimated with polychotomous logistic regression models including all the variables listed in the table. RB: respiratory bronchiolitis; OCIP: other chronic interstitial pneumonia; UIP: usual interstitial pneumonia.

- HRCT findings in 692 smokers: abnormalities in 158 (23%),

3% UIP-like changes,

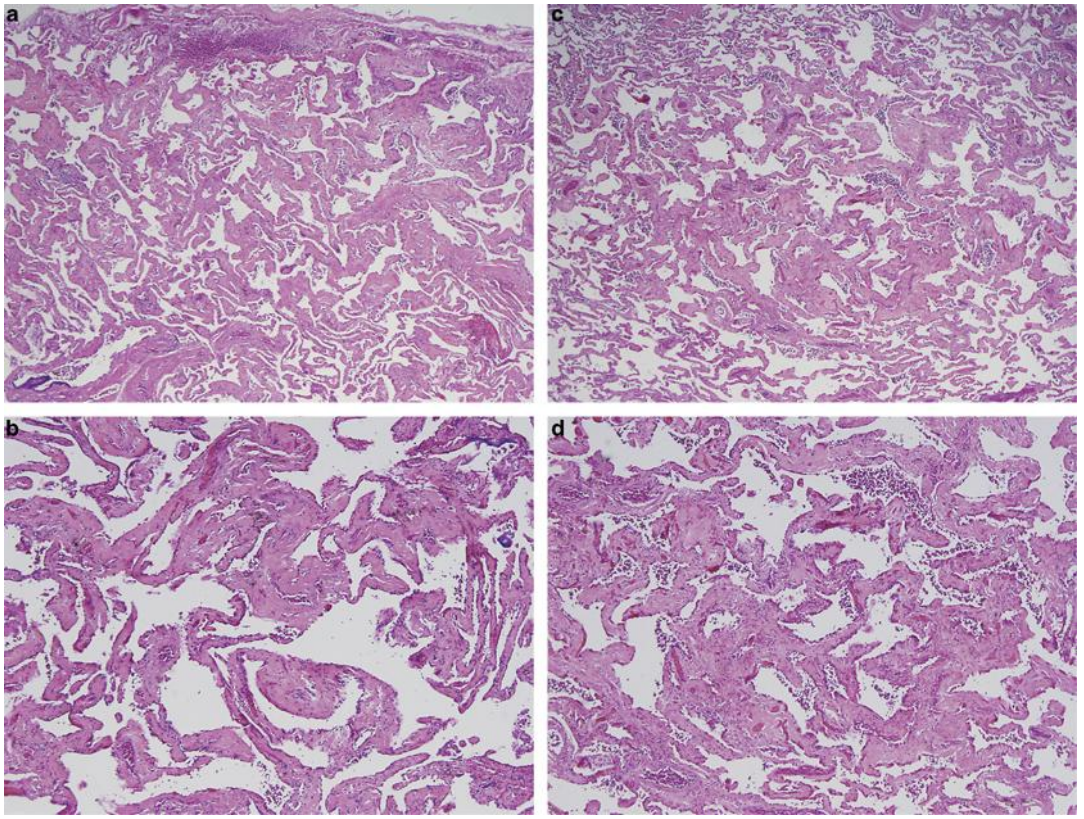
3.8% other interstitial pneumonia patterns,

15.7% RB and 3% with indeterminate changes

Sverzellati N, et al. Eur Respir J 2011; 38: 392-400.

Epidemiology of SRIF

- Subtle interstitial changes increasingly recognizable by improved radiographic techniques



Katzenstein AL, et al. Modern Pathology 2012; S1: S68-78.

Epidemiology of IPF

Table 2 Prevalence and incidence of idiopathic pulmonary fibrosis by geography

Geography	Study year(s)	Prevalence (per 100,000)	Incidence (per 100,000/y)	Case ascertainment
United States				
New Mexico[12] (Bernalillo County)	1988–1990	13.2–20.2[a]	7.4–10.7[a]	Population-based, multiple sources ICD-9 516.3
Twenty states[13]	2000	14.0–42.7[b]	6.8–16.3[b]	Private insurance claims database ICD-9 516.3
Minnesota[14] (Olmsted County)	1997–2005	27.9–63.0[b]	8.8–17.4[b]	Population-based medical record linkage system (2000 ATS/ERS criteria)
Europe				
Czech Republic[17]	1981–1990	6.5–12.1[c]	0.74–1.28[c]	Clinical registry
Norway[18]	1984–1998	23.4	4.3	Hospital district records ICD-8 and 9 codes and record review
Finland[19]	1997–1998	16–18	–	Pulmonary clinics and hospital database ICD-10 J84.1, subset reviewed (2000 ATS/ERS criteria)
Greece[8]	2004	3.4	0.9	Survey of pulmonary practices (2000 ATS/ERS criteria)
UK[15]	1991–2003	–	4.6	Nation-wide primary care database
UK[16]	2000–2009	–	7.4	Nation-wide primary care database
Turkey[9]	2007–2009	–	4.9[d]	Survey of pulmonary practices (2000 ATS/ERS criteria)
Asia				
Taiwan[20]	1997–2007	0.7–6.4[e]	0.6–1.4[e]	National health insurance database ICD-9 516.3
Japan[11]	2005	2.9[f]	–	Medical benefits records and subset medical record review for IIPs

Notes: [a]Range reported for women and men, respectively; [b]range reported for narrow and broad case definitions; [c]range reported for rates over the study period; [d]incident cases for ILD reported as 25.8 per 100,000/y, where 19.9% were IPF; [e]range reported for the broad definition over the study period; [f]prevalence reported for all IIPs as 3.4 per 100,000, of which 85.7% were reported to be IPF.

Abbreviations: ATS, American Thoracic Society; ERS, European Respiratory Society; ICD-8, -9, -10, International Classification of Disease-eighth, ninth, or tenth revisions; IIP, idiopathic interstitial pneumonia; y, year; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis.

Ley B, et al. Clin Epidemiol 2013; 5: 483-492.

Epidemiology of IPF

Table 3 Proposed risk factors for idiopathic pulmonary fibrosis

Environmental/occupational
Agriculture/farming
Birds
Hairdressing
Livestock
Animal/vegetable dust
Textile dust
Mold
Metal dusts
Wood dusts
Stone/sand/silica
Wood fires
Tobacco smoke
Genetic mutations
TERT, TERC (telomerase genes)
SPC (surfactant protein C)
SPA2 (surfactant protein A2)
MUC5B (mucin 5B)
ELMOD2 (ELMO domain-containing 2)
TOLLIP (toll interacting protein)
Comorbidity
Gastroesophageal reflux disease
Diabetes mellitus
Infection
Human herpes viruses
Hepatitis C virus

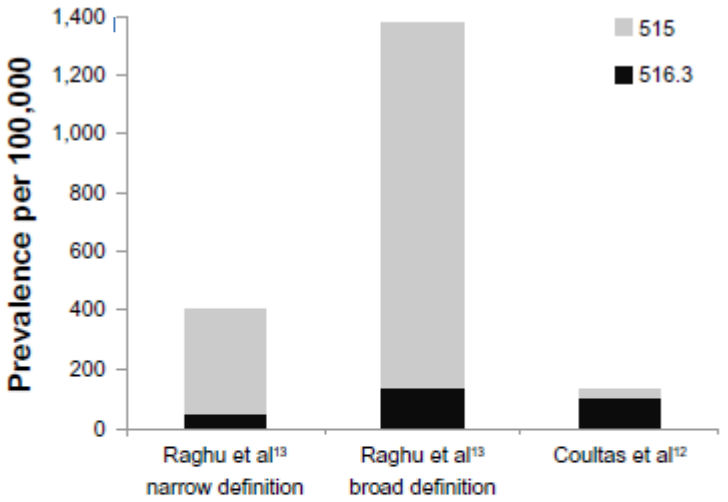
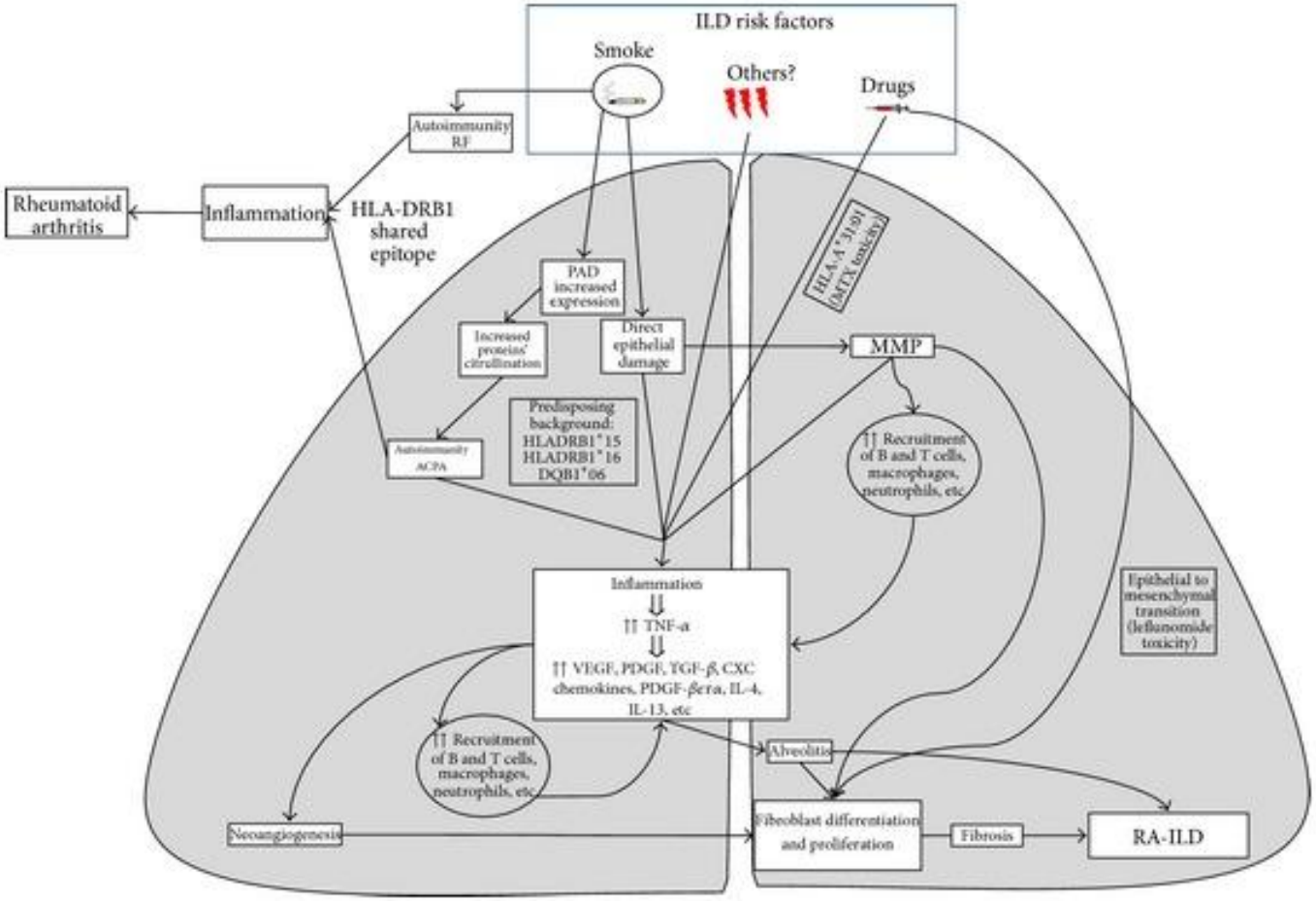


Figure 1 The prevalence of idiopathic pulmonary fibrosis varies widely depending on case definitions in epidemiologic studies.
Notes: There is marked variation with the use of ICD-9 code 515 (postinflammatory pulmonary fibrosis) and/or ICD-9 code 516.3 (idiopathic fibrosing alveolitis) to identify cases, with or without added levels of stringency. The Raghu et al broad definition required the presence of ICD-9 code 516.3 or 515 and exclusion of other diagnoses that cause interstitial lung disease. The Raghu et al narrow definition required the broad definition plus additional procedure codes for lung biopsy and radiology studies. The Coultas et al cases were drawn from multiple administrative and clinical sources. Estimates are shown for men in the 65–74 year age group from Raghu et al[13] and Coultas et al[12].

Ley B, et al. Clin Epidemiol 2013; 5: 483-492 .

Epidemiology of CTD-ILD



Cavagna L, et al. Biomed Res Int 2013;2013:759760.

Epidemiology of CTD-ILD

- Estimates of RA-ILD prevalence - 4% to 30%, incidence 4.1 per 1,000 people with RA
- Median survival RA-ILD 2.6 years versus 9.9 years of RA patients without ILD
  - ILD progression with respiratory failure and direct RA complications
  - ILD 6–13% of the excess mortality of RA patients compared to the general population
- Median survival of 60 months in RA-ILD ; 27 months in IPF

Cavagna L, et al. Biomed Res Int 2013;2013:759760.

Epidemiology of CPFE

- 5-10% ILD patients
- Upper lobe emphysema + interstitial pneumonia (84% UIP, fibrotic NSIP)

Fibrotic changes	
Honeycombing	58 (95)
Reticular opacities	53 (87)
Traction bronchiectasis	42 (69)
Ground-glass opacities	40 (66)
Architectural or bronchial distortion	24 (39)
Emphysema	
Centrilobular emphysema	59 (97)
Paraseptal emphysema	57 (93)
Bullae	33 (54)

Cottin V, et al. Eur Respir J 2005; 26: 586-93.

Epidemiology of CPFE

Table 2. Characteristics of and pulmonary function test results for patients with CPFE in the context of CTD, patients with idiopathic CPFE, and patients with ILD and CTD without emphysema*

	CPFE and CTD (this series)	CPFE without CTD (from ref. 1)	ILD and CTD
No. of men/no. of women	23/11	60/1†	10/24‡
Age, years	57 ± 11 (36–75)	65 ± 10 (36–84)‡	52 ± 16 (18–73)
Smoking status, no. of patients, current/former/never	10/20/4	19/42/0	5/8/20†
Pack-years of smoking	39 ± 23 (7–100)	46 ± 27 (5–120)	23 ± 19 (3–50)†
FVC, % predicted	85 ± 24 (40–146)	90 ± 18 (47–125)	71 ± 21 (25–133)§
FEV_1, % predicted	76 ± 20 (39–118)	80 ± 21 (33–123)	71 ± 22 (26–128)
FEV_1/FVC, %	73 ± 15 (19–98)	69 ± 13 (30–94)	81 ± 8 (65–98)§
Total lung capacity, % predicted	82 ± 17 (53–125)	88 ± 17 (44–132)	68 ± 12 (36–93)†
Residual volume, % predicted	87 ± 32 (33–189)	90 ± 32 (35–188)	63 ± 18 (34–106)‡
DLCO, % predicted	46 ± 16 (22–92)	37 ± 16 (10–80)‡	53 ± 19 (22–110)§
KCO, % predicted	60 ± 13 (37–94)	46 ± 19 (8–84)†	79 ± 22 (43–123)†
PaO_2 at rest, kPa	9.9 ± 1.3 (7.2–12.7)	8.4 ± 1.9 (4.6–13.3)	10.7 ± 1.3 (8.3–13.5)§
$PaCO_2$ at rest, kPa	5.1 ± 0.6 (3.9–6.0)	4.9 ± 0.7 (3.0–7.3)	5.3 ± 0.5 (4.3–6.2)
6-minute walk distance, meters	373 ± 138 (0–528)	336 ± 139 (50–548)	408 ± 125 (190–654)
SpO_2 after 6-minute walk test, %	88 ± 7 (73–97)	85 ± 6 (74–96)	87 ± 7 (71–97)
Decrease in SpO_2 during 6-minute walk test, %	−4 ± 6 (−19–6)	−9 ± 6 (−20–0)	−8 ± 7 (−28–0)
Composite physiologic index	41 ± 14 (14–65)	46 ± 12 (17–66)	43 ± 16 (7–72)

* Except where indicated otherwise, values are the mean ± SD (range). Patients in the group with interstitial lung disease (ILD) and connective tissue disease (CTD) were matched with the patients in the present series for a diagnosis of CTD. FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; DLCO = diffusing capacity for carbon monoxide; KCO = single-breath transfer coefficient of the lung for carbon monoxide; SpO_2 = peripheral oxygen saturation.
† $P < 0.001$ versus combined pulmonary fibrosis and emphysema (CPFE) and CTD.
‡ $P < 0.01$ versus CPFE and CTD
§ $P < 0.05$ versus CPFE and CTD.

Cottin V, et al. Arthritis Rheum 2011;63:295-304.

Epidemiology of Goodpasture syndrome

- Prevalence 1 in 1,000,000 to 1 in 2,000,000 in European population
- 18-30 years, 50-65 years, male 6x more often than female
- 85% active smokers
- Initiation of GP disease - conformational transition in crosslinked or uncrosslinked hexamers forming GP neoepitopes
- Post-translational modifications (nitrosylation, glycation), oxidation damage or proteolytic cleavage
- Conformational changes in the formation of the pathogenic neoepitopes
- Smoking or exposure to organic solvents - increasing the proportion of uncrosslinked hexamers that are more susceptible to conformational transitions

Pedchenko V et al. Curr Opin Nephrol Hypertens 2011;20:290-6.

Smoking cessation


NO SMOKING
BEYOND
THIS POINT