# IPFJES in context, radiological UIP with a history of occupational asbestos exposure: IPF, asbestosis, and 25 fibre/ml.years

## Introduction

Diagnostic criteria for IPF and asbestosis can be difficult to apply in patients with a history of radiological UIP and occupational asbestos exposure. Here I briefly review how IPF and asbestosis are diagnosed and how this has changed. Then I examine the history of '25 fibre-ml' years in relation to asbestosis and appraise its utility in attributing UIP to asbestos in the context of the IPFJES findings.

### How IPF is diagnosed

Historically, that which is now called IPF has been otherwise known. For example, in 1971 cryptogenic fibrosing alveolitis (CFA) was defined by Turner-Warwick and Haslam(Turner-Warwick and Haslam 1971) as applying to patients with:

1. no identifiable cause for lung fibrosis identified on the basis of detailed occupational and clinical history
2. widespread irregular shadowing on chest xray and widespread crackles on auscultation
3. if a biopsy was performed then histological features of alveolar fibrosis and the absence of granuloma or intra alveolar organisation or evidence of pneumoconiosis

Turner-Warwick(Turner-Warwick 1998) acknowleges potential difficulties in establishing attribution and causality in IPF. She observes that there is variation in clinical practice with respect to the standard applied to exclude IPF; some clinicians exclude IPF when exposure to a potential cause is identified, others only when there is clear exposure to an established cause.

As technologies such as high resolution computed tomography (HRCT) became widely available and our understanding of idiopathic interstitial pneumonias developed diagnostic nomenclature have been updated. Most signifi-

cantly, in 2000, an international consensus definition of IPF as UIP on HRCT +/- biopsy in an idiopathic setting was reached. Wells 2018(Wells et al. 2018) provides a detailed discussion of the evolution of modern IPF nomenclature. The 2011 joint ERS/ATS guidelines(Raghu et al. 2011), current at the initiation of IPFJES, state that the diagnosis of IPF requires:

1. exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity).
2. the presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy
3. specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy

Surgical lung biopsy for the diagnosis of IPF has been much less frequently performed since it was shown to be unecessary in the context of typical radiological and clinical findings(Hunninghake et al. 2001) and to carry a significant mortality and morbidity risk.(Utz et al. 2001)(Lettieri et al. 2005)

In the UK, National Institute for Clinical Excellence (NICE) clinical practice guidelines recommend that the diagnosis of IPF is made at a multidisciplinary team meeting which (minimally) includes a chest physician, a radiologist, and a histopathologist, with expertise in ILD. This approach resulted in moderate inter-rater agreement among UK physicians in a international case-cohort study, weighted kappa 0.61 (0.50-0.67), and good prognostic accuracy, median hazards ratio for death comparing IPF to non-IPF ILD was 2.76 (1.97-3.69).(Walsh 2017)

### How asbestosis is diagnosed

The first report of fibrosis of the lungs due to inhalation of asbestos dust(Cooke 1924) appeared in the British Medical Journal in 1924 and described the case of Nellie Kershaw, an English textile worker from who worked for Turner Brothers Asbestos spinning raw asbestos fibre into yarn. Kershaw died aged 33 years and was found to have extensive lung fibrosis and asbestos fibres at post mortem, having worked with asbestos textiles since age 13. The inquest into her death led to a parliamentary enquiry that formally acknowledged the existence of asbestosis and this in turn led to the introduction of asbestos industry regulations in 1931.(Tweedale 2000)

Asbestos industry regulations included the provision of independent medical boards to diagnose asbestosis. By the 1960s asbestosis was diagnosed by medical boards based on a history of asbestos exposure from working in a "scheduled area", part of an asbestos factory where a manufacturing process such as carding was carried out, plus two positive findings from the following:

1. the presence of basal rales
2. finger-clubbing
3. radiological appearances and pulmonary function studies

The medical boards have been subject to criticism for their conservatism, financial links to asbestos industry, and failure to protect workers.(Tweedale and Hansen 1998)

In 1963, a statement from the Committee on the Pneumoconiosis of the Council of on Occupational Health of the American Medical Association discusses asbestosis and suggests diagnosis should be, as with other pneumoconiosis, based on:

1. an appropriate occupational history; hazardous substance is present in patients work environment and they have been significantly exposed to it
2. abnormal roentgen shadows
3. compatible clinical picture (accepting that symptoms, for example progressive exertional dyspnoea, will rarely be distinctive enough to support diagnosis)

In 1986, a statement from the American Thoracic Society on the diagnosis of nonmalignant diseases related to asbestos(Murphy et al. 1986) recommended that the term asbestosis should be reserved for interstitial fibrosis of the pulmonary parenchyma in which asbestos bodies or fibres may be demonstrated. However, they acknowledge that clinically the diagnosis of asbestosis must be made without the benefit of histological examination of lung tissue since lung biopsy is rarely indicated or carried out. They suggest that indirect methods of asbestos exposure must be used and that the diagnosis does not require any measurable impairment of lung function or physical disability to be present. Specific necessary clinical diagnostic criteria suggested are:

1. A reliable history of exposure
2. An appropriate time interval between exposure and detection

Optional additional criteria suggested are:

1. Chest roentgenographic evidence of type “s”, “t”, “u”, small irregular opacifications of profusion 1/1 or greater
2. A restrictive pattern of lung impairment with a forced vital capacity below the lower limit of normal
3. Bilateral late or pan inspiratory crackles at the posterior lung bases not cleared by cough

with a recommendation that emphasis be given to radiological findings.

In 1997 The International Expert Meeting on Asbestos, Asbestosis, and Cancer was convened in Helsinki to discuss asbestos related lung and pleural disorders and to agree diagnostic criteria.(Tossavainen 1997) They point out that neither asbestos associated clinical features nor architectural tissue abnormalities sufficiently differ from other causes of interstitial fibrosis to allow confident diagnosis without a history of significant asbestos exposure or the detection of asbestos fibres or bodies in the lung greatly in excess of that commonly seen in the general population. The 1997 guideline introduces cumulative occupational asbestos exposure of 25 fibre-ml years as the being associated with a 2-fold increase in lung cancer risk and the level at which clinical cases of asbestosis may occur.

The 1997 report(Tossavainen 1997) also recommends adoption of the Roggli-Pratt modification of the CAP-NIOSH system for the histological grading of asbestosis(Sporn and Roggli 2004) and, in relation to histological grading, the 2014 update(Wolff et al. 2015) cites 2010 diagnostic criteria from the Asbestosis Committee of the College of American Pathologists and Pulmonary Pathology Society.(Roggli et al. 2010) These diagnostic criteria include discussion of a 25 fibre-ml years exposure threshold for diagnosis of asbestosis. The authors acknowledge that biopsy is seldom required but argue that when it is undertaken asbestos bodies are required for a histological diagnosis of asbestosis. The 2014 update(Wolff et al. 2015) has been criticised for claiming that a confident diagnosis of asbestosis can not be made without the presence of a history of asbestos exposure or the presence of asbestos bodies. The inclusion of reference to a cumulative exposure 25 fibre-ml years is criticised both because of uncertainties about the evidence base for the threshold and because of concern that it is impractical for clinicians to implement, there not being a well established means to arrive at a fibre-ml year estimate. The requirement for demonstration of asbestos bodies is criticised

because of known variability in the biopersistence of inhaled asbestos fibres and limitations of quantification methods.(Baur et al. 2016)

### Radiological UIP with a history of occupational asbestos exposure: IPF, asbestosis, and 25 fibre/ml.years

If one accepts that IPF is a diagnosis of exclusion and can only be made after alternative causes of lung fibrosis such as asbestosis are excluded then making a confident diagnosis of asbestosis becomes key. Writing in Thorax over 20 years ago Turner-Warwick(Turner-Warwick 1998) raised an important potential difficulty in IPF diagnosis. Specifically, that there is variation in clinical practice with respect to the standard applied to exclude IPF; some clinicians exclude IPF when exposure to a potential cause is identified, others only when there is clear exposure to an established cause.

Determining if asbestos exposure is a potential or established cause of an individual's UIP is non-trivial. Successive asbestosis diagnosis guidelines have consistently recognised that the clinical features of and radiological findings in seen in asbestosis are insufficiently distinct from other causes of interstitial fibrosis to allow confident diagnosis without a history of significant asbestos exposure or the detection of asbestos fibres in the lung. They have also acknowledged both that individual genetic susceptibility factors are important determinants of disease risk, but these are not well characterised and not tested in routine clinical practice, and that it is seldom justified to obtain tissue biopsy for the purposes of asbestosis diagnosis. The result is that assessing whether a patient has a history of significant asbestos exposure becomes the key diagnostic criteria.

Logically, there are four prerequisites to assessing whether an individual patient has a history of significant (enough to cause fibrosis) asbestos exposure.

1. The relationship between asbestos exposure and asbestosis risk must be known, specifically how much exposure is required for how much risk?
2. A means of assessing the amount of asbestos exposure an individual patient has had
3. Knowledge of individual susceptibility factors and the magnitude of risk that they carry

4. An agreed level of risk for attributing fibrosis to asbestos exposure rather than calling it idiopathic or attributing it to another inhaled fibrogenic exposure e.g silica

Issues include unreliability of historic measurements and diagnoses, changed workplace exposure and demographic of potential cases, lack of good comparator group data to compare the exposure of cases against, and incomplete data on individual genetic susceptibility factors, particularly in relation to gene-environment interaction, severely limit the task.

The 1984 report of the Royal Commissionon on matters of health and safety arising from the use of asbestos in Ontario(Dupré 1984) suggests 25 fibre-ml years as a 'best guess' for the level of exposure below which fibrotic process cannot advance to the point of clinical manifestation based on previous studies.

However the report also admits significnt the limitations of studies of asbestos exposure and asbestosis incidence including instruments used to measure ambient exposure, duration of follow up, and measurement of co-exposures such as silica or smoking. And recognises the importance of host suceptibility:

"We recognize that among some cohorts studied, even workers in the lower cumulative exposure categories have died as a result of asbestosis. We recognize too that variations in susceptibility among individuals make it difficult to have any confidence in a no-effect or threshold level."

It is interesting to consider whether in such a circumstance (of lower levels of asbestos exposure in the population) host suceptibility factors become more important. IPFJES data appear to support this. The majority of individuals with UIP in IPFJES do not have 'heavy', defined as greater than 25 fibre-ml years, asbestos exposure, in line with progressive asbestos exposure regualation leading to a reduction in population asbestos exposure.

We find evidence of interaction between carriage of the minor allele of MUC5b rs35705950, smoking,and asbestos exposure, to increase risk of UIP. Furthermore, we find that the magnitude of this risk is greater for those with 'heavy' exposure. This has parallels with the Geofrey Roses' prevention pararadox; the majority of cases of disease come from a population at low or moderate risk of that disease, and only a minority of cases come from the high risk population (of the same disease) because the number of people at high risk is small.(Rose 1981)

But what to do pragmatically with respect to diagnosis?

The approach taken potentially affects a large number of people. Interstitial lung abnormalities including UIP are increasingly recognised as a common feature on CT of the lung in older individuals, occurring in 4-9% of smokers and 2-7% of non-smokers.(Hatabu et al. 2020) Many interstitial lung abnormalities may be described as having an indeterminate for UIP pattern(Hunninghake 2019) compatible with a diagnosis of IPF(Raghu et al. 2018) (or asbestosis).

IPFJES found the majority (over 60%) of cases, and controls, to have been ever exposed to asbestos, defined as ever having a job that was medium or high risk for asbestos exposure on the basis of proportional mortality data for pleural mesothlioma.(Peto et al. 2009)

It's possible that genetic susceptibility factors are interacting with asbestos to cause UIP which, if known, might be properly called asbestosis. This appears to be the case with minor allele of MUC5b rs35705950 and smoking in IPFJES. However, something other than asbestos might also be causing UIP, which, if it can't be known is properly called IPF. With no observable difference in rates of asbestos exposure between cases and controls, and no knowledge of individual suceptibility, diagnosisng IPF seems the more parsimonious thing to do. Further study of potential genetic-asbestos interaction in patients with UIP is needed to fully understand the contribution asbestos makes to disease risk.

## Conclusion

IPF and asbestosis are hard to distinguish because there are frequently few or no distinguishing features clinically, including on the basis of an exposure history, or on CT, and a biopsy not usually done. There is clear practice variation in the standard applied to exclude IPF; is identification of a potential cause sufficient or is clear exposure to an established cause necessary?

When the potential cause being considered is asbestos difficulties arise because it is difficult to quantify asbestos exposure (and relatedly to accurately diagnsose asbestosis) so the relationship between asbestos exposure and risk of asbestosis is ill-defined, host suceptibility to asbestos is known to be important but gene-environment interactions are poorly characterised and patients

are not usually genotyped, and there is not clear agreement on the level of risk asbestosis (and corresponding exposure) required for diagnosis.

One might argue that an individual with UIP who has any degree of asbestos exposure has asbestosis due to asbestos interacting with assumed host suceptibility factors. One might equally argue that an individual with UIP who has any degree of asbestos exposure does not have asbestosis because asbestos exposure alone does not appear to make any significant contribution to UIP at a population level for current levels of asbestos exposure and there is insufficient evidence for asbestos interaction with host suceptibility factors being an important contributer to UIP.

IPFJES tells us that a history of asbestos exposure alone does not increase risk of UIP but that in concert with smoking and genetic suceptibility factors it does increase risk, and that this increase in risk is greater for more heavily exposed individuals. We are left to decide our thresholds for using the identification of asbestos as a potential cause of UIP in an individual as a reason to exclude IPF, and to diagnose asbestosis, with limited data.

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