Is occupational asbestos exposure an under-recognised cause of idiopathic pulmonary fibrosis?

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A thesis presented for the degree of
Doctor of Philosophy

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I, Carl Jonathan Reynolds confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

The question of whether occupational asbestos exposure is an under-recognized cause of idiopathic pulmonary fibrosis arises because it is clinically plausible, epidemiologically plausible, and consistent with fibre studies and case-control data. This thesis examines the question by means of a literature review and a novel hospital based case-control study, the idiopathic pulmonary fibrosis job exposures study (IPFJES).

Acknowledgements

I am grateful to Zeinab, Ada, and Rosa for putting up with me.

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I am grateful to the partcipants, to Rupa and all of the principle investigators and their teams for making the study happen.

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Abbreviations

- **IPF** Idiopathic pulmonary fibrosis.
- **MUC5B** Mucin 5B gene.

Chapter 1

Introduction to thesis

1.1 Occupational asbestos exposure as an underecognised cause of idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a progressive, fibrotic lung disease which in 2012 was the recorded cause of death for c.4000 people in England and Wales. Its incidence, currently around 7.5/100,000 person-years, has increased by 5% pa since 2000.[1] The pathophysiology of IPF is complex, the outcome of host susceptibility factors, epithelial injury, and a dysregulated repair process. Several gene polymorphisms which result in a vulnerable alveolar epithelium have been characterized; they include abnormalities in mucin genes (eg MUC5B), surfactant protein genes, and telomerase genes (eg TERT and TERC).[2][3][4] The median age of onset is 70 years and the condition is more common in men (M:F ratio 1.6), manual workers, and those living in industrial areas[1], patterns that are not unique to the UK.[3] The prognosis is poor, with a median survival of three years.[5][6]

These epidemiological distributions of IPF are consistent with a long-latency response to occupational dust exposure; in particular, the incidence of IPF correlates strongly (if ecologically) with historic asbestos use.[7] Mineralogical studies support the concept of asbestosis-IPF misclassification by revealing high fibre burdens in the lung tissue of patients diagnosed with 'IPF' and revision of the diagnosis to 'asbestosis'.[8][9][10][11]

Identification of occupational asbestos fibre exposure as an under-recognised cause of IPF is important to improve our understanding of the aetio-pathophysiology of IPF and the accuracy of prognostic information. It would have implications for compensation and impact on the current restrictions on individual treatment. Importantly, it would inform evidence-based workplace exposure policies in the UK and internationally, particularly in the many countries with continuing high levels of asbestos use.

1.2 Aims and objectives

My overall aim is to characterize and measure asbestos exposure as an occupational determinant of IPF; additionally, I will determine host-exposure interactions mediated by candidate susceptibility polymorphisms (in particular MUC5B promoter polymorphism rs35705950).

My specific research questions are:

1. Does a dose-response relationship exist for occupational asbestos exposure and IPF?
2. Does the presence of asbestos exposure modify the association between IPF and rs35705950?

Chapter 2

Data sources

- For the literature review and meta-analysis of occupational exposures in IPF I consider all published IPF case-control studies reporting on occupational exposures.
- For the mortality analysis I use data obtained from the Office of National Statistics, Health and Safety Executive, and the World Health Organisation Mortality Database.
- Brief reviews of asbestos exposure assessment and genetic suceptibility in IPF rely on the published literature.
- Primary case-control data collected during my PhD as part of the idiopathic pulmonary fibrosis job exposures study (IPFJES) is used to analyze asbestos exposure in IPF. (?include navaratum case control jobs data that was shared)

2.1 Outline of thesis

This chapter (Chapter 1) describes the problem studied, aims and objectives, and approach. Chapter 2 is a literature review and meta-analysis of IPF case-control studies that report on occupational exposure. Chapter 3 is an analysis of IPF and asbestos related disease mortality data. Chapter 4 is a review of asbestos exposure assessment methodology. Chapter 5 is a review of genetic suceptibility in IPF. Chapter 6 describes the idiopathic pulmonary fibrosis job exposures study including results and analysis arising from it. Chapter 7 concludes the thesis by summarising it and suggesting future work.

Chapter 3

Literature review and meta-analysis

3.1 Introduction

Idiopathic pulmonary fibrosis (IPF) is a diagnosis of exclusion. It is made in the presence of a usual interstitial pneumonitis (UIP) pattern on high resolution CT scan or biopsy. The diagnosis requires that known causes of interstitial lung disease (such as drug toxicity, connective tissue disease, domestic, and occupational or environmental exposures) be excluded.[12]

Attributing a disease process to a specific exposure can be difficult. Disease processes are frequently complex or multifactorial, depending on the interaction of genetic and environmental components. Well-studied and relatively frequent entities such as chronic obstructive pulmonary disease, ischaemic heart disease and diabetes lend themselves to epidemiologic investigation, delineating the major risk factors for disease and their relative contributions to risk at the population level. IPF presents an additional challenge to attribution; because of its relative infrequency, epidemiologic study of the disease is largely limited to case-control studies.[13] Studying specific occupational exposures also presents its own challenges; co-exposure is common, occupational hygeine data is frequently limited and self-reported exposure is prone to recall bias.

I identified several review articles of the epidemiology of interstitial lung disease that do not necessarily focus on IPF and only briefly mention occupational factors (e.g Ley2013[3]. Here I consider review articles that specifically deal with occupational factors in IPF and cite the case-control studies used.

Turner-Warwick (1998) discusses 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. She explains that diagnosis based on radiologic and clinical findings, and not on lung biopsy or bronchioalveolar lavage, may result in initiating agents for disease being overlooked. Further, that exposures such as asbestos, silica, coal, graphite, hard metal, and avian proteins, may result in disease that can not be differentiated from IPF.[14]

Reviewing the epidemiology of IPF and case-control studies to date Hubbard (2001) describes the association of IPF with occupational exposures to metal and wood and estimates that 10% of IPF cases may be due to occupational metal exposure and 5% of cases to wood.[15]

Taskar and Coultas (2006) review and carry out a meta-analysis of six case-control studies investigating environmental and occupational exposures in IPF. They report population attributable risk percentages for agriculture and farming (20.8%), livestock (4.1%), wood dust (5%), metal dust (3.4%), stone/sand/silica (3.5%), and smoking (49.1%).[16]

Gulati and Redlich's (2015) review of exposures causing usual interstitial pneumonia highlights that asbestosis may appear indistinguishable from IPF and summarises previous case-control studies but did not pool studies to perform a meta-analysis.[17]

I sought to identify and meta-analyze all IPF case-control studies dealing with occupational exposures.

3.2 Method

Pubmed, embase, and google scholar search engines were searched for combinations of the terms 'idiopathic pulmonary fibrosis', 'occupation', 'case-control study' and synonyms. When relevant papers were identified papers referenced and papers citing the paper were reviewed. Medline ranker[18] and bespoke pubmed 'mining' techniques[19] were also used.

Two investigators independently reviewed and abstracted data for five exposure categories common to the identified case-control studies: "vapors, gases, dusts, and/or fumes (VGDF)", "metal dust", "wood dust", "silica dust", and "agricultural dust". We calculated PAF as follows: PAF=pc(OR - 1)/OR, where pc is the proportion of cases exposed and OR is the risk estimate.

We calculated pooled OR and pooled PAF for occupational exposures using fixed effects models and random effects models in Stata. When there was results of the models differed substantively, we used the results of the fixed effects model, which were more conservative. The pooled PAF relied on the ratio of attributable cases to all cases underlying each risk estimate.

3.3 Results

We found (as of May 2017) 14 case-control studies looking at occupational exposures in IPF (Table 3.1) the most recent review article covers only eight of them. Associations with metal, wood, silica, and agricultural dust were reported. [20][21] [22] [23] [24] [25] [26] [27] [28] [29] [30] [31]

43 risk estimates from 14 publications (2027 IPF cases in total) were used. Each exposure category was assessed with 6-11 risk estimates (Table 3.2).

3.4 Discussion

tables above will need updating becaue of gremlins

Table 3.1: Summary of IPF case-control studies investigating occupational exposures

Reference (n cases)	OR; 95% CI					PAF %					Case Definition	Exposure Measure
	vgdf*	metal	wood	ag	si	vgdf*	metal	wood	ag	si		
Scott 1990(40)	1.3; 0.8, 2.0	11.0; 2.3, 52.0	2.9; 0.9, 9.9	10.9; 1.2, 96.0	1.6; 0.5, 4.8	17	12	10	12	15	clinical assessment, CXR, pulmonary function	questionnaire
Iwai 1994(86)		1.3; 1.1, 1.6		3.0; 1.3, 7.4							clinical assessment, CXR or CT, pulmonary function	questionnaire
Iwai 1994(615)	2.0; 1.2, 3.1										autopsy	job group
Hubbard 1996(218)		1.7; 1.1, 2.7	1.7; 1.0, 2.9		1.8; 1.0, 3.1	10	6				clinical assessment, CXR or CT, pulmonary function	questionnaire and telephone interview
Mullen 1998(15)	2.4; 0.7, 8.4		3.3; 0.4, 25.8		11; 1.1, 115	23		7		20	clinical assessment, lung biopsy or CT	questionnaire
Baumgartner 2000(248)		2.0; 1.0, 4.0	1.6; 0.8, 3.3	1.6; 1.0, 2.5	3.9; 1.2, 12.7		5	3	7	3	clinical assessment, lung biopsy or BAL, CT	telephone interview
Hubbard 2000(22)		1.1; 0.4, 2.7				5					death certificate diagnosis	job group
Miyake 2005(102)		9.6; 1.7, 181.1	6.0; 0.3, 112.4		1.8; 0.5, 7.0	26	11	4		11	clinical assessment, lung biopsy or BAL, CT	questionnaire
Gustafson 2007(140)	1.1; 0.7, 1.7	0.9; 0.5, 1.6	1.2; 0.7, 2.2		1.4; 0.7, 2.7	6		3		10	pulmonary fibrosis of unknown aetiology + requiring LTOT	questionnaire
Garcia-Sancho Figueroa 2010(97)	1.2; 0.8, 1.9				9						clinical assessment, CT +/- lung biopsy	questionnaire
Garcia-Sancho 2011(100)	2.8; 1.5, 5.5				5						clinical assessment, CT +/- lung biopsy	questionnaire
Awadalla 2012(201)		1.6; 0.7, 3.6	2.7; 1, 16.8	1.3; 0.7, 2.0	1.1; 0.5, 2.7		6	7	7	13	clinical assessment, CT, pulmonary function	questionnaire
Paolocci 2013 (abstract only)(65)		2.8; 1.1, 7.2			2.0; 0.9, 4.4		9	2		22	clinical assessment and CT	questionnaire
Koo 2017(78)	2.7; 0.7, 10.9	5.0; 1.4, 18.2	2.5; 0.5, 12.3		1.2; 0.4, 3.8	35	22	5		27	clinical assessment, CT +/- lung biopsy	interview

Table 3.2: Pooled estimates of occupational contributions to IPF (based on 12 case-control studies)

Exposure	Risk estimates (n)	Pooled OR (95% CI)	Pooled PAF (95% CI)
VGDF*	8	1.6 (1.3-1.9)	14 (12-17)
Metal dust	10	1.4 (1.3-1.7)	8 (6-10)
Wood dust	11	1.7 (1.3-2.2)	4 (3-5)
Agricultural dust	6	1.8 (1.0-3.1)	8 (5-10)
Silica dust	9	1.7 (1.3-2.3)	7 (5-9)

Our results support the case for a proportion of IPF cases being attributable to occupational exposures.

Pooled ORs were significantly elevated for VGDF, metal dust, wood dust, agricultural dust, and silica dust; the pooled PAF estimates by category ranged from 4-23%. This is an important finding for an otherwise idiopathic disease which carries significant morbidity and mortality; identifying causal occupational agents would permit remidiation and prevention.

Associations between IPF and wood, metal, and agricultural dust were previouly reported in a meta-analysis of six case-control studies by Taskar and Coultas. [16] While our findings are similar we found a smaller effect size for agricultural exposure and a large effect size for non-specific vapours, gases, dust, and fumes (VGDF), see Table 3.2.

Funnel plot asymmetry using Egger's test, which may be due to publication bias, was present for VGDF ($p = 0.04$) and metal dust ($p = 0.03$) but not for wood dust ($p = 0.09$), silica dust ($p = 0.2$), and agricultural dust ($p = 0.6$). However, the number of studies included is small and funnel plot assymetry may be due to chance rather than bias.

There are several limitations to the meta-analysis that arise from the case-control studies included.

Several studies [20] [32] [24] [26] [28] used population controls but do not provide details on participation rates. Participation rates can be low for community controls; a recent UK case-control study investigating prothrombotic factors in IPF reported a response rate of 28% for commumnity controls. [33] This approach is vulnerable to non-responder bias. One study[34] used employee occupational records and death certificates from pension-fund records for a single company and was only able to locate the occupational records for 40% of cases and 38% of controls.

Nearly all studies relied on self-reported exposures rather than life time occupational histories to assess exposure; an approach that is prone to recall bias and does not permit examination of dose-response relationships.

Reliance of self-reported exposures also means that studies are potentially vulnerable to confounding as a result of co-exposure. For example, several studies have described strong associations between metal work and IPF and specify sheet metal workers[21][20][34], a group who are frequently exposed to dust containing asbestos fibres[35] and who in a recent UK study, had the highest risk of mesothelioma.[36]

Case definitions and sources for cases varied between studies. For example Scott (1990)[20] used a case definition which included a chest radiograph showing bilateral interstitial shadowing whereas most other studies relied on high resolution CT. Four studies used mortality data [21][37][26][34] to identify cases and one study[26] used a national register of patients recieving oxygen therapy. Differences in healthcare coverage and coding practices can result in selection bias.[38]

3.5 Conclusion

The observed excess risk could represent disease misclassification of pneumoconiosis or hypersensitivity pneumonitis, but this is unlikely to fully explain the observed effects. Our analysis supports an etiologic role for occupational exposures in IPF, potentially explaining up to 23% of the burden of disease and highlighting a role for workplace exposure reduction in disease prevention.

Chapter 4

Mortality analysis

4.1 Introduction

The incidence of Idiopathic pulmonary fibrosis (IPF) has been increasing at a rate of 5% per annum since 2000. By definition, the diagnosis of IPF is not made in the presence of an identifiable cause. However, the distribution of the disease in the population (more common in men, manual workers, and those living in more industrial areas of the country) suggests a causal contribution from an occupational or environmental source.

It is hypothesised that a proportion of Idiopathic Pulmonary Fibrosis (IPF) cases are due to occult environmental or occupational exposures to asbestos dust. This would be expected to result in a spatio-temporal association between IPF, Mesothelioma, and Asbestosis mortality patterns coinciding with asbestos exposure. It would also be expected to produce a birth cohort effect

Our aim was to examine trends in IPF, Mesothelioma, and Asbestosis mortality data for evidence of cohort effect and association.

4.2 Method

Regional age and sex stratified mortality data for IPF, Mesothelioma, and Asbestosis were obtained for England and Wales from the Office of National Statistics for the period 1974–2012. Data were age-standardised and visualised using the Python Pandas data analysis library and matplotlib.

4.3 Results

IPF mortality continues to rise. Female:Male is approximately 1:1.6. There are more IPF deaths in the North West and South East of England. IPF mortality does appear to correlate with mesothelioma mortality (Figure 4.1). There is evidence of a cohort effect with age-specific IPF death rates increasing in successive cohorts, most clearly seen from age 60 (Figure 4.2). While overall rates were higher for men but there were not marked sex differences in cohort mortality trends.

4.4 Discussion

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4.5 Conclusion

Conclusions: The birth cohort effect we observed is consistent with a proportion of IPF cases being due to an occupational or environmental exposure with latency and further research is needed.

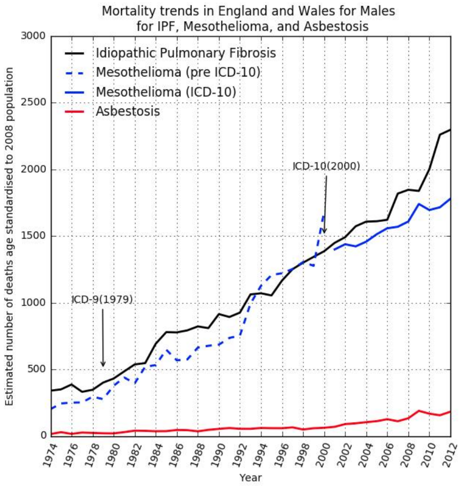

Figure 4.1: IPF, mesothelioma, and asbestosis mortality trends

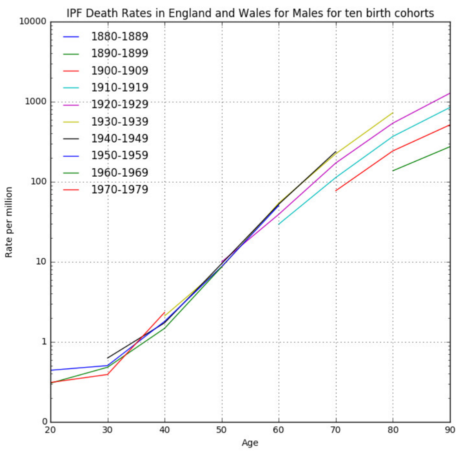

Figure 4.2: IPF male birth cohorts

Chapter 5

Asbestos exposure assessment

5.1 Introduction

Asbestos related respiratory disease is initiated by inhalation of asbestos fibres. In the UK clinically significant asbestos exposure is largely occupational and, as a result of asbestos control legislation, historic. Occupational exposure can be assessed quantitatively by sampling ambient air at a workplace and calculating a fibre count using microscopy. Alternatively, because asbestos fibres persist in tissues they can also be sampled by lung biopsy or bronchoalveolar lavage.

Historic workplace measurments are a valuable resource for assessing exposure but are pauce and dependant on working practices and measurment technique at the time assessment.

5.2 Method

5.3 Results

5.4 Discussion

5.5 Conclusion

in tissue/bal/etc

Most previous work has relied on self-reported workplace exposure information, an approach that is open to recall bias and deals poorly with confounding.

Lifetime occupational histories are more accurately recalled than self-reported workplace exposures and can be combined with measures such as mesothelioma occupational mortality proportionate mortality (PMR) estimates and job-process assessments to minimize recall bias and more accurately characterise cumulative exposures. [39][40][41][36] This allows too the examination of 'exposure-response' relationships, entirely lacking in the published literature.

Chapter 6

Genetic susceptibility in IPF and MUC5b

6.1 Introduction

Third, advances in our understanding of IPF susceptibility now permit study of host-exposure interactions. The minor-allele of the rs35705950 SNP in the mucin 5B gene was found to be present in 38% of IPF patients but just 9% of controls.[42] The polymorphism results in excess MUC5B protein in the airway, impaired clearance of inhaled substances and a chronic inflammatory burden on the alveolar surface.[42] The association is allele dose-dependent, has been replicated in independent cohorts, and appears to confer improved survival.[3][42][43] Two large GWASs have confirmed the observed associations of IPF with MUC5B and other loci.[44][45]

6.2 Method

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6.3 Results

6.4 Discussion

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6.5 Conclusion

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Chapter 7

Idiopathic pulmonary fibrosis job exposures study (IPFJES)

7.1 Introduction

My study will be a multi-centre, hospital-outpatient, incident case-control study. Participants will be recruited from a UK network of six confirmed centres. Cases will be men who present, between 07.2017 and 07.2019, with a new diagnosis of IPF consistent with standard criteria[46]; they will be identified monthly by the MDT coordinator of participating centres.[47]

For each case, four controls, frequency-matched on age, will be randomly selected from incident outpatient attendances (not confined to respiratory) who do not have a diagnosis of IPF and are from the hospital as the case. Monthly lists of outpatient attendances will be obtained using the patient administration systems of participating centres. 120 cases and 480 controls will be recruited over two years with four participants enrolled and interviewed per day.

Eligible participants will be contacted by telephone and invited to participate. An interviewer will collect data on demographics, lifetime occupational history, hobbies, family medical history, and smoking using a structured web-based questionnaire designed by us to collect lifetime occupational histories.

This approach will facilitate coding, allow input validation, and permit questions to be tailored to pre-specified conditions. The questions will be developed in collaboration with an international expert in asbestos exposure measurement, Dr John Cherrie of the IOM. Participants will be invited to provide a venous blood sample for genetic analysis.

Cases and controls will be genotyped using a panel of 15 pre-defined candidate susceptibility SNPs including rs35705950. Genotyping will be undertaken using Q-PCR and Taqman assays on DNA isolated from whole blood samples.

For the primary analysis unconditional logistic regression will be used to analyse ‘any’ vs ‘no’ asbestos exposure and categories of cumulative exposure adjusting for age and smoking status. Prior data[36] indicate that the probability of exposure among controls is 0.29. If the true OR for disease in exposed subjects relative to unexposed subjects is 2.0, I will need to recruit 94 case patients and 376 control patients to be able to reject the null hypothesis that this odds ratio equals 1 with $\beta = 0.2$ and $\alpha = 0.05$[48]; my planned sample size sample size includes a margin for model stability and incomplete data.[49]

Secondary (exploratory) analysis will investigate gene-environment interaction. The global minor allele frequency of MUC5B rs35705950 is 0.05.[50] With an estimated prevalence of IPF of 20/100000[1] and with ORs 2.0 for asbestos exposure and 6.8 for rs35705950[42], 113 cases would be required to detect a minimum interaction OR of 4.0.[51] While I acknowledge that this exploratory analysis will have the power to detect only a large effect size it seems a valuable opportunity to examine an unexplored area in IPF research.

7.2 Method

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7.3 Results

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7.4 Discussion

possibility of missed chronic HP [52]

7.5 Conclusion

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Chapter 8

Conclusion

8.1 Thesis summary

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8.2 Future work

chronic hp

Appendix 1: IPF epidemiology code

IPF epidemiology

Appendix 2: IPFJES study documentation

IPFJES study documentation

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