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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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 aetiopathophysiology 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?

1.3 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.

1.4 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 2

Literature review and meta-analysis

2.1 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]

There are many review articles of the epidemiology of interstitial lung disease that do not necessarily focus on IPF and only briefly mention occupational factors. We selected review articles that specifically deal with occupational factors in IPF and cite the case-control studies and case-reports identified.

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.[13]

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.[14]

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%).[15]

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.[16]

2.2 Method

Background: Optimal strategies to extract relevant content from Pubmed for occupational lung disease topics are not clearly defined and the utility of mining techniques has not been assessed. Aims and objectives: To evaluate, given a 'seed' of known relevant papers (here 12 occupational IPF case-control studies), the use of relative citation ratio (RCR)[1], jaccard similarity(JS)[2] and coverage(C) to identify additional relevant papers. Methods: We used the python programming language and the Pubmed application programming interface to extract all papers citing the 'seed' papers and to calculate and sort by RCR, JS, and C. Full analysis online.[3] Results: Papers citing 'seed' papers sorted by RCR, JS, and C. Table 1 and Figure 1. Conclusions: Pubmed mining techniques can help to identify additional relevant papers.

2.3 Results

We found (as of May 2017) 14 case-control studies looking at occupational exposures in IPF (Table \ref{metatable1]); the most recent review article covers only eight of them. Associations with metal, wood, silica, and agricultural dust were reported. [17][18] [19] [20] [21] [22] [23] [24] [25] [26] [27] [28]

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.

In all, 43 risk estimates from 14 publications (2027 IPF cases in total) were used. Each exposure category was assessed with 6-11 risk estimates. Pooled ORs were significantly elevated for each category; the pooled PAF estimates by category ranged from 4-14% (Table \ref{metatable2]). We found funnel plot asymmetry using Egger's test, which may be due to publication bias, for VGDF ($p = 0.04$) and metal dust ($p = 0.04$) but not for wood dust ($p = 0.1$), 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. ## Discussion

2.4 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 14% of the burden of disease and highlighting a role for workplace exposure reduction in disease prevention.

Chapter 3

Mortality analysis

3.1 Introduction

Mortality from Idiopathic Pulmonary Fibrosis in England and Wales by birth cohor

Introduction and objectives: 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. This would be expected to produce a cohort effect. Our aim was to examine trends in IPF mortality data for evidence of such an effect.

The recent publication of the INPULSIS1, INPULSIS2, and ASCEND trials mean that meaningful treatment for patients with IPF beyond palliation or lung transplantation is an emergent possibility. But for a history of asbestos exposure, IPF and Asbestosis may produce a clinically identical picture with progressive breathlessness and a Usual

Interstitial Pneumonia on CT or hisotopathologic examination. A history of asbestos exposure may be easily missed and several authors have hypothesised that a proportion of IPF may be due to occult asbestos exposure. New

antifibrotic treatments for IPF throw the question of whether or not a proportion of IPF is due to occult asbestos exposure into sharp focus; patients known to have Asbestos Exposure are currently not considered to be candidates for antifibrotic treatments and it may be timely to revisit this. These data show national and regional correlations, and marked sex differences, which are supportive of the hypothesis that a proportion of IPF is due to Occult Asbestos Exposure and provide motivation for further studies in this area.

Background: It is hypothesised that a proportion of Idiopathic Pulmonary Fibrosis (IPF) cases are due to occult environmental or occupational exposures to asbestos dust. Aims and objectives: To investigate a possible association between IPF, Mesothelioma, and Asbestosis mortality consistent with asbestos exposure. To visualise agestandardised annual mortality trends for IPF, Mesothelioma, and Asbestosis for men and women.

3.2 Method

Methods: Age and sex stratified mortality data for IPF 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.

We present new data obtained from the Office of National Statistics for England and Wales on the annual number of deaths due to IPF, Mesothelioma, and Asbestos for the period 19742012 broken down by age, sex, and region.

3.3 Results

Results: There is evidence of a cohort effect with age-specific IPF death rates increasing in successive cohorts, most clearly seen from age 60. Overall rates were higher for men but there were not marked sex differences in cohort mortality trends (data not shown).

Results: IPF mortality continues to rise. Female:Male is approximately 1:1.6.

Figure 3.1 shows a figure.

3.4 Discussion

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3.5 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.

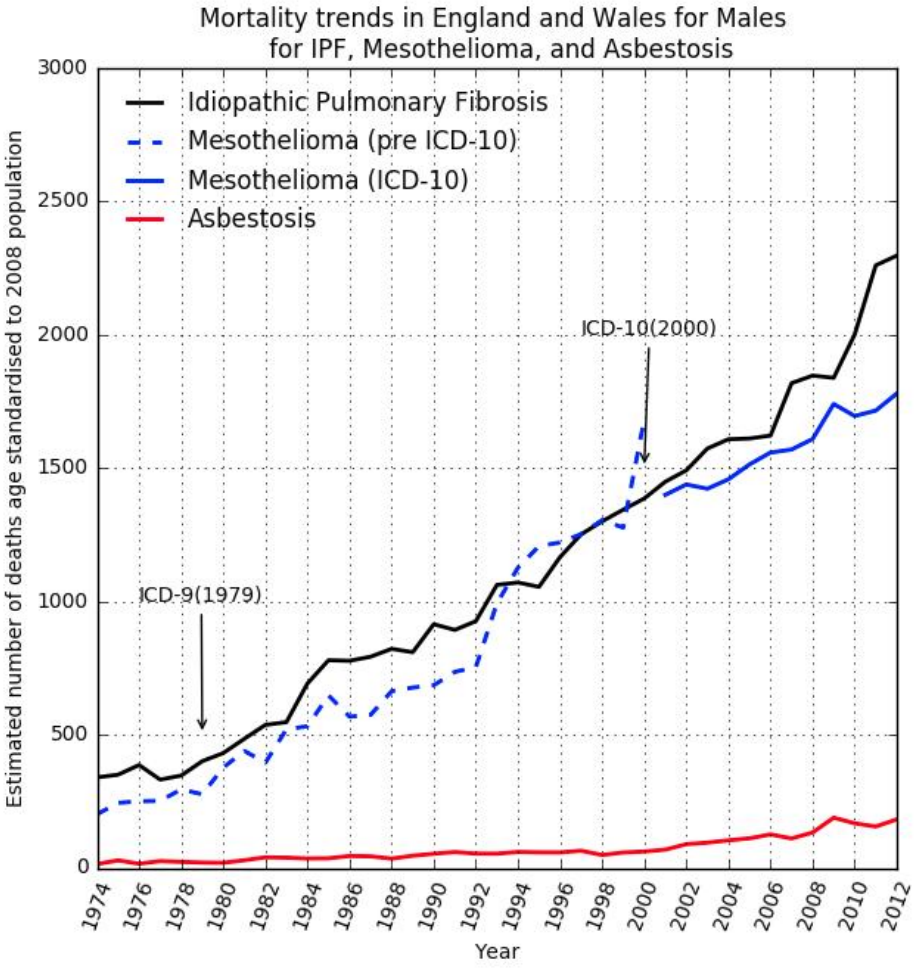

Figure 3.1: IPF, mesothelioma, and asbestosis mortality trends

Chapter 4

Asbestos exposure assessment

4.1 Introduction

In addition to its epidemiological and clinical plausibility there are several additional reasons why study of this area is needed. First, most previous work relied on self-reported workplace exposure information, an approach that is open to recall bias and deals poorly with confounding; for example, studies have described strong associations between metal work and IPF and specify sheet metal workers[18][17][29], a group who are frequently exposed to dust containing asbestos fibres[30] and who in a recent UK study, had the highest risk of mesothelioma.[31] Lifetime occupational histories are more accurately recalled than self-reported workplace exposures and can be combined with measures such as proportionate mortality (PMR) estimates and job-process assessments to minimize recall bias and more accurately characterise cumulative exposures. [32][33][34][31] This allows too the examination of 'exposure-response' relationships, entirely lacking in the published literature.

4.2 Method

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Chapter 5

Genetic susceptibility in IPF

5.1 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.[35] The polymorphism results in excess MUC5B protein in the airway, impaired clearance of inhaled substances and a chronic inflammatory burden on the alveolar surface.[35] The association is allele dose-dependent, has been replicated in independent cohorts, and appears to confer improved survival.[3][35][36] Two large GWASs have confirmed the observed associations of IPF with MUC5B and other loci.[37][38]

5.2 Method

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5.3 Results

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Chapter 6

Idiopathic pulmonary fibrosis job exposures study (IPFJES)

6.1 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[39]; they will be identified monthly by the MDT coordinator of participating centres.[40]

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[31] 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 $\alpha = 0.05$[41]; my planned sample size sample size includes a margin for model stability and incomplete data.[42]

Secondary (exploratory) analysis will investigate gene-environment interaction. The global minor allele frequency of MUC5B rs35705950 is 0.05.[43] With an estimated prevalence of IPF of 20/100000[1] and with ORs 2.0 for asbestos exposure and 6.8 for rs35705950[35], 113 cases would be required to detect a minimum interaction OR of 4.0.[44] 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.

6.2 Method

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6.5 Conclusion

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Chapter 7

Conclusion

7.1 Thesis summary

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7.2 Future work

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Appendix 1: Some extra stuff

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Appendix 2: Some more extra stuff

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