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

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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] Clinical, radiological and histopathological findings in asbestosis and IPF are similar[8][9]. Mineralogical studies support the concept of asbestosis-IPF mis-

classification by revealing high fibre burdens in the lung tissue of patients diagnosed with 'IPF' and revision of the diagnosis to 'asbestosis'.[10][11][12][13]

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. (?include navaratum case control jobs data that was shared)

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: how much IPF is attributable to occupational exposures?

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.[14]

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.[15] 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.[16]

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.[17]

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%).[18]

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.[19]

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

2.2 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 a relevant papers was identified papers referenced and papers citing the paper were reviewed. Medline ranker[20] and bespoke pubmed 'mining' techniques[21] 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.

2.3 Results

We found (as of May 2017) 15 case-control studies looking at occupational exposures in IPF the most recent review article covers only eight of them. Associations with metal, wood, silica, and agricultural dust were reported. [22] [23] [24] [25] [26] [27] [28] [29] [30] [31] [32] [33] [34] [35] [36]

40 risk estimates from 12 publications (1326 IPF cases in total) were used (Table 3.1)[22] [24] [25] [26] [27] [28] [29] [31] [32] [33] [34] [36]

Three studies were not used, one because data was not collected on the proportion of cases with specific occupational exposures[23], one because of methodological differences in exposure assignment[30], and one because if reported data for pulmonary fibrosis rather than IPF.[35]

Each exposure category was assessed with 6-11 risk estimates (Table 3.2).

2.4 Discussion

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. [18] 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 [22] [37] [26] [29] [32] 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 con-

Table 2.1: Summary of IPF case-control studies investigating occupational exposures

Reference (n cases)	**OR; 95% CI**					**PAF %**				
	vgdf*	metal	wood	ag	si	vgdf*	metal	wood	ag	si
Scott 1990(40)[?]	1.3; 0.8, 2.0	11.0; 2.3, 52.4	2.9; 0.9, 9.9	10.9; 1.2, 96.0	1.6; 0.5, 4.8	17	12	10	12	5
Hubbard 1996(218)[?]		1.7; 1.1, 2.7	1.7; 1.0, 2.9				10	6		
Mullen 1998(15)[?]	2.4; 0.7, 8.4		3.3; 0.4, 25.8		11; 1.1, 115	20		7		20
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	2
Hubbard 2000(22)[?]		1.1; 0.4, 2.7					5			
Miyake 2005(102)[?]	5.6; 2.1, 17.9	9.6; 1.7, 181.1	6.0; 0.3, 112.4	0.6; 0.2, 1.9	1.8; 0.5, 7.0	26	11	4	0	5
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	0	3		3
Garcia-Sancho Figueroa 2010(97)[?]	1.2; 0.8, 1.9					9				
Garcia-Sancho 2011(100)[?]	2.8; 1.5, 5.5					50				
Awadalla 2012 men (95)[?]		1.6; 0.7, 3.6	2.7; 1.1, 6.8	1.0; 0.4, 2.3	1.1; 0.5, 2.7		6	9	0	1
Awadalla 2012 women (106)[?]			4.3; 0.8, 22.1	3.3; 1.2, 10.1				6	14	
Paolocci 2013 soft wood (abstract only)(65)[?]		2.8; 1.1, 7.2	1.1; 0.4, 3.3		2.0; 0.9, 4.4		9	0		11
Paolocci 2013 hard wood (abstract only)(n/a)[?]			0.9; 0.3, 2.8					0		
Kao	2.7;	5.0;	2.5;		1.2;	35	22	5		5

trols. [38] This approach is vulnerable to non-responder bias. One study[27] 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[23][22][27], a group who are frequently exposed to dust containing asbestos fibres[39] and who in a recent UK study, had the highest risk of mesothelioma.[40]

Case definitions and sources for cases varied between studies. For example Scott (1990)[22] 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 [23][30][29][27] to identify cases and one study[29] used a national register of patients recieving oxygen therapy. Differences in healthcare coverage and coding practices can result in selection bias.[41]

2.5 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 3

Mortality analysis: do mortality trends support an occupational cause?

3.1 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.

3.2 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.

3.3 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 3.1). There is evidence of a cohort effect with age-specific IPF death rates increasing in successive cohorts, most clearly seen from age 60 (Figure 3.2). While overall rates were higher for men but there were not marked sex differences in cohort mortality trends.

3.4 Discussion

icd coding chat

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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.

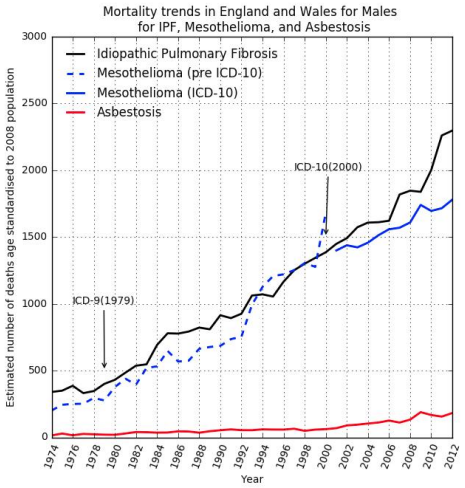

Figure 3.1: IPF, mesothelioma, and asbestosis mortality trends

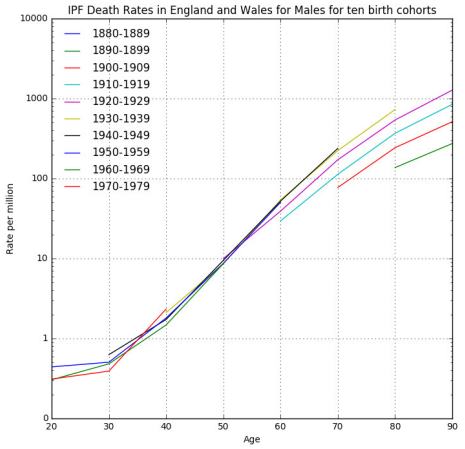

Figure 3.2: IPF male birth cohorts

Chapter 4

Historic asbestos exposure assessment: can it be done?

4.1 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 asbestos exposure can be assessed quantitatively by sampling ambient air at a workplace and calculating a fibre count using microscopy. Alternatively, because inhaled asbestos fibres persist in the lung they can be sampled by lung biopsy, bronchoalveolar lavage, or at autopsy.

Historic workplace measurements are a valuable resource for assessing exposure but are limited in several ways. Measurements are not available for many occupations, where measurements are available they are dependant on working practices and measurement technique at the time of assessment; they do not necessarily generalize well.

Measurement of asbestos fibres in lung tissue by means of biopsy or bronchoalveolar lavage is invasive and both procedures carry the risk of serious complication including death. Additionally, the biopersistance of asbestos fibres is variable, counts are sensitive to techniques used, and establishing

appropriate references ranges is challenging.[42]

Expert assessment and exposure modelling approaches integrate historic workplace measurements with simulated workplace measurements and an individuals recollection of job processes he or she has carried out during their working life.[43]

Job-exposure matrices (JEMs) are widely used in occupational epidemiology studies to assess exposure to potential hazards. These assign levels of exposure to health hazards on the basis of job title.

Finally, self-reported exposures are a subjects direct report of what they have been exposed to, these are usually elicited by questionnaire or at interview.

The asbestos exposure assessment literature presents difficulties for review because it is large and recognised to be at risk of bias as a result of its economic importance to powerful industrial and medicolegal actors[44].

Here we critically review different means of historic asbestos exposure assessment and consider their clinical and research utility.

4.2 Method

We searched pubmed and google scholar for combinations and synonyms of "asbestos", "exposure assessment", together with terms for modes of assessment including "lung biopsy", "bronchoalveolar lavage", "exposure reconstruction", and "job-exposure matrix". When a relevant papers was identified, papers referenced, and papers citing, the paper were reviewed.

4.3 Results

4.3.1 Lung biopsy and bronchoalveolar lavage

The first report of fibrosis of the lung due to asbestos dust[45] included a description of the post mortem microscopic appearances of the lungs which

showed abundant asbestos fibres in areas of fibrosis.

The demonstration of asbestos fibres on lung biopsy in the context of pulmonary fibrosis is clearly supportive of the diagnosis of asbestosis. However, a failure to demonstrate fibres can not be used to rule out asbestos exposure because fibres, particularly chrysotile fibres, may be cleared from the lung and counting methods have a significant false-negative rate.[42]

Despite this recent 2014 Helsinki guidelines[46] and UK Royal College of Pathologists guidelines appear to suggest that a clear history of substantial occupational asbestos exposure is insufficient for diagnosis and that the absence of asbestos bodies or fibre counts above a certain threshold might be used to rule out the diagnosis. The shortcomings of such an approach highlighted above are also described by responses to the Helsinki guideline.[47][48][49]

Lung biopsy carries significant health risks, particularly for patients who already have compromised lung function and it can not be justified solely on medico-legal grounds.[48] Therefore, the clinical utility of lung biopsy and bronchoalveolar lavage is limited to ruling in asbestosis when a suggestive exposure history and radiology are lacking.

In a research context lung biopsy and bronchoalveolar lavage have provided valuable population level insights. Lung biopsy asbestos fibre counts have been examined in a UK case-control study where mesothelioma cases were compared with lung cancer controls. Fibre counts were found to be higher in groups with greater occupational risk (as defined by PMR), providing additional support for the pre-eminence of an occupational history.[40][50] In a follow up study asbestos fibre counts from unselected surgically treated pneumothorax patients were used to demonstrated that population amphibole burden is falling and is proportional to mesothelioma mortality.[51]

A similar correlation with occupational exposure history, overall downward trend in fibre counts, and a significant false negative rate has been observed in a recent Belgian study of patients undergoing bronchoscopy with broncheoalvelolar lavage sampling for asbestos fibre quantification.[52]

4.3.2 Historic workplace measurements

Occupational hygienists have recorded a large numbers of workplace measurements of asbestos in different settings, at different times, using a variety of different means. These measurements reside in national databases such as the HSE National Exposure Database[53], and EV@LUTIL[54], in the published literature, and in unpublished company records.

The use of different means of making workplace assessments results in difficulties with respect to the accuracy and comparability of measurements. For example, instruments that count particles rather than asbestos fibres have been used and there is no established conversion factor.[55] Phase contrast microscopy has also been used which is less sensitive that scanning electron microscopy, which is in turn less sensitive than transmission electron microscopy and energy-dispersive x-ray analysis.[56]

Where era and task specific workplace exposure data matching a particular patient occupational history is available and readily deniable it is a valuable means of assessing exposure history. Unfortunately, in practice measurements are usually limited to the subset of jobs thought to be potentially harmful "high" exposure jobs at the time of measurement. As awareness of the sources and harm of asbestos exposure has developed overtime the available data, until the use of asbestos was banned in the UK, is also skewed to more recent times.[57][58]

Measurements have found greater utility in a research setting where they can help to quantify risk and inform regulatory policy and compliance in specific workplace settings, for example, in car mechanics[59] or skilled craftsmen.[60]

4.3.3 Exposure reconstruction

Sahmel et al[58] propose a seven-step framework (see Figure 4.1) which they use to enumerate and critique exposure reconstruction approaches.

Reconstruction techniques may be quantitative, semi-quantitative, or qualitative. Quantitative exposure reconstruction bases exposure estimates on

data from similar (historic or current) exposure scenarios or simulation studies. Semi-quantitative exposure reconstruction bases exposure estimates on exposure data matrices (using a job-exposure matrix) and/or exposure determinants (using an exposure model). Qualitative exposure reconstruction bases exposure estimates on the expert judgement of an industrial hygienist and self reported exposures.[58]

4.3.3.1 Job-exposure matrices

Several job-exposure matrices that deal with asbestos have been reported. Pannett et al's 1985 job-exposure matrix for use in population studies in England and Wales[61] found good agreement between job-title assigned categories of exposure (none, low, moderate, high) for asbestos and direct review of the original occupational history by an expert.

Rake et al[40] assigned categories risk of exposure (low, medium, high) using occupational mortality statistics for pleural mesothelioma. Because pleural mesothelioma in men is nearly entirely attributable to occupational asbestos exposure, pleural mesothelioma is rapidly fatal, and death certificates record occupation in addition to cause of death, the proportional mortality ratio for pleural mesothelioma (number of deaths due to pleural mesothelioma/total number of deaths) can serve as proxy for average asbestos exposure in a particular occupation. This approach has been validated in the same cohort by amphibole fibre counts.[50]

DOM-JEM[62] was developed for use in population based multi-centre lung

Figure 4.1: Seven step framework for exposure reconstruction

cancer case-control study. It assigns job titles one of three categories of asbestos exposure (no exposure, low exposure, high exposure) based on the consensus of three independent expert raters. DOM-JEM showed poor agreement with expert assessment ($\kappa = 0.17$) but less heterogeneity. In a study applying DOM-JEM to the Netherlands Cohort Study (NCS) DOM-JEM showed poor agreement with expert assessment (K = 0.29).[63]

The Finish Information System on Occupational Exposure (FINJEM)[64] covers exposure to 84 different agents, including asbestos, for 311 jobs across 9 periods spanning 1945-2015. Era-specific estimates of the mean level of asbestos exposure are available for 27 jobs based on expert assessment and measurement data; the exact details of the grounds for estimates are kept in a proprietary FINJEM database which is not freely available. FINJEM showed poor agreement with expert assessment of asbestos exposure ($\kappa = 0.23$) but reasonable identification of mesothelioma risk when evaluated using the NCS.[63][65]

AsbJEM[66] was developed in Australia by an expert panel of three industrial hygienists using all available exposure data. It is based on FINJEM and provides quantitative estimates of annual exposure for 224 occupations across three time periods spanning 1943 to 2004. It also showed poor agreement with expert assessment of asbestos exposure ($\kappa = 0.10$)

SYN-JEM[67] describes a JEM developed for four carcinogens. It provides quantified asbestos exposure estimates based on 27958 personal measurements (spanning 1971-2009), a mixed effects statistical model, and a priori categorical assessment of exposure (none, low, high). Cherrie et al[68] point out that SYN-JEM provides little contrast in the modelled exposure level between categories as the geometric mean for low jobs was 0.061 fibres/ml and for high jobs 0.074 fibres/ml and that there are wide variations in regional estimates that are difficult to explain.

JEMS are generally taken to be superior to direct questions about exposures because they are cheaper, have greater validity, and are less vulnerable to differential recall. This is because recall of occupations is not influenced by disease status, coding of occupation is blind to case-control status, and translation of codes into exposure is standardized and can not be influence

by disease status of a subject.[69][70][71]

Orlowski et al[72] compared two JEMs with a structured job specific questionnaire (SQ) in a lung cancer case-control study. They found that agreement between the JEMs and the SQ was poor ($\kappa = 0.23 - 0.27$) and suggested that the sources of error for JEMs were loss of information due to the use of job codes as surrogates for job task descriptions and the insufficiency of published data on occupational asbestos exposure.

JEMs are not routinely used in clinical practice because they are not usually available or accessible for specific patients. In a research setting they are frequently helpful though in addition to the strengths and weaknesses outlined about the desirability of reusing an existing JEM vs developing a study specific JEM must be considered.

4.3.3.2 Exposure modelling approaches

Exposure modelling approaches modify existing measurement data on the basis of knowledge of the determinants of exposure. They may be viewed as the formalization of professional decision criteria used by hygienists in their assessment of workplace exposures.[57]

A common conceptual framework for this is the source-receptor model source receptor model[73][57] whereby inhalation exposure is considered in terms of an exposure source, a pathway from source to receptor, and the receptor. The model is then used to propose modifying factors such as activity emission potential, substance emission potential, localized control, worker behavior, surface contamination and respiratory protection.[73].

In the hands of some hygienists assessment of historic asbestos exposure based on interview can correlate well with amphibole fibre counts.[74] By extension, exposure modelling approaches, using industrial hygienist methods, might be expected to be useful. Exposure modelling approaches make strong intuitive sense; it is known that there is significant within-worker and between-worker variability in occupational exposures[75] and, for example, room size and ventilation have been empirically shown to affect the concen-

tration of airborne chemical exposures.[76] Further, mathematical exposure models that take account of known exposure modifying factors to estimate past exposures have shown a good correlation with measured values.[43]

A quantified validated historic asbestos exposure model[68] has recently been developed and proposed as a means of for risk stratifying asbestos exposed workers to optimize mesothelioma screening efforts. The approach has the advantage, compared with job-exposure matrices, of providing a more granular quantified exposure assessment, sensitive to the exposure circumstances of the individual. However, the approach is limited by the fact that the individual must recall that they must recall their exposure circumstances which due to the latency of asbestos related disease may have occurred over 30 years ago. The approach is also limited by the relatively small number of industry-specific data points used for validation, though is unavoidable because of the scarcity of exposure measurement data.

Exposure modelling approaches to assessing asbestos exposure have research and clinical utility notwithstanding the limitations outlined above together with the requirement that assessors be appropriately trained.

4.3.3.3 Self-reported exposure

Self-reported exposures are a subjects direct report of what they have been exposed to. Typically this is elicited by asking about a specific exposure via questionnaire or interview. Differential recall of self-reported exposures according to disease status is a concern but few studies have found evidence of this and it appears to be less of an issue when prompted responses, rather than volunteered, responses about occupational exposures are used.[77]

Most studies comparing self-reported exposures to industrial hygiene measurements have found significant associations but with wide variation in the proportions of variance explained by the self reports. This is not surprising given that it is known there is significant within-worker and between-worker variability in occupational exposures.[70][75]

Studies comparing self-reported exposures to expert assessment find highly

variable levels of agreement ($\kappa - 0.05 - 0.94$) with a median $\kappa 0.6$. In two studies comparing self-reported exposures with JEMs, self-reported exposures were more sensitive and of similar or worse specificity.[70]

Self-reported exposures have been shown to be more accurate for easily sensed exposures such as solvents with a strong smell, dusts with larger particle sizes, and vibrations that can be felt. Providing a reference point, for example using well known machines from a workplace to gauge noise category also improves accuracy.[70]

Self-reported exposures have clinical utility in that they can suggest or support consideration of an occupational cause for disease. Ideally such self-reports are combined with the clinicians knowledge of the likely occupational exposures given the occupational history and other available data to strengthen or weaken the case as appropriate. Similarly, they have utility in a research setting where they may augment other means of assessment.

4.4 Discussion

The accuracy of historic asbestos exposure assessment, by any means, is limited by the paucity of occupational asbestos measurement data, measurement technique limitations, within and between worker exposure variability, and participant recall. There does not exist a universally agreed "gold standard" against which to evaluate methods. Accurate quantified assessment of historic exposure, where evidence is scarce, may be an impossible task.[78]

Nonetheless, clinically, historic asbestos exposure assessments must be made for attribution. Specifically, to inform whether the required threshold of asbestos exposure (as assessed by various means) has been crossed so it is possible to say that, for example, scarring of the lung with an usual interstital pneumonia pattern in an individual patient is caused by asbestos exposure. This carries medicolegal in addition to scientific importance and has not been well established by any assessment method.

In the context of mesothelioma case-control studies fibre-counts do at least provide an objective means of assessing historic asbestos exposure against

which other means can be compared. It is encouraging that industrial hygienist assessment and assessment using job title and PMR correlates strongly with fibre counts.[71][50] Further and more generally, it is encouraging that estimates from explicit asbestos exposure modelling systems such as Cherrie et al's[68], show good correlation with measurement data.

4.5 Conclusion

Quantitative estimates of historic occupational asbestos exposures will generally have high uncertainty. However, less precise measures, such as relative difference in exposure among epidemiological groups may be quite certain even though the numerical estimates are only approximate. This is invaluable in studies examining aetiological hypothesis.[57]

Chapter 5

MUC5b + environmental insult = IPF?

5.1 Introduction

5.1.1 Mucus, Mucins, MUC5b: structure, function and evolutionary importance

Mucus is an essential part of the innate immune system, considered to be universal within most phyla of both aquatic and terrestrial metazoans. It plays a pivotal role in the prevention of disease by serving as an antimicrobial barrier, it also has physiological functions including allowing the exchange of oxygen, carbon dioxide, nutrient and metabolites, lubricating surfaces and reducing damage due to sheer, reducing dehydration of the epithelia and providing the polymeric matrix which enables ciliary-mucus particle transport. Mucus barriers are essential for the separation and protection of an organism from its external environment, and likely a prerequisite for the exclusion of bacteria from bodily tissues and evolution of gastrointestinal and respiratory tracts. The importance of mucus barriers is further underlined when one considers the energy investment continuous mucus production and release requires; for example, corals use mucus to trap particles and transport them towards their mouths and the reef-building coral Acropora acuminata

is thought to dedicate up to 40% of its daily net carbon fixation to this task alone.[79] Mucins are a key component of mucus, they are highly evolutionary conserved large glycoproteins that date back around 600 million years to Nematostella vectensis, the starlet sea anemone, which is an early marine invertebrate. The earliest human mucin analogue is found in Xenopus tropicalis, the African clawed frog, which evolved about 300 million years ago and mucins are the likely explanation for the observation that frogs show such great resistance to infection during dissection and it has been shown that knockdown of mucin in the skin mucus barrier of Xenopus tropicalis tadpoles leads to susceptibility to infection by the opportunistic pathogen Aeromonas hydrophila.[80]

The mucin family is composed of proteins that contain tandom repeat structures with a high proportion of prolines, threonines, and serines; the PTS domain. It is further defined by extensive glycosylation of the PTS domain through N-Acetylgalactosamine O-linkages at the threonine and serine residues.[81] The resultant oligisaccharide chains and polymeric structure create the viscoeleastic properties of mucus which confer its barrier properties and play an important role in storage and secretion. [79] Mucins are 50-90% carbohydrate and they are anionic because most of their terminal sugars contain carboxyl or sulphate groups. Mucin glycan helps to sequester pathogen by acting as a 'decoy' and providing sites for microbial adhesins to bind; for example, human salivary MUC5b interacts with streptococcal species, and patterns of glycosylation change during inflammation.[82][83] Mucin barriers can be subverted by pathogens, strategies include production of enzymes to degrade mucin core proteins and mucin carbohydrates, and evolution of effective motility through mucus gels - many mucosal bacterial pathogens are flagellated for this reason. There is evidence that degradative enzymes are required for pathogenesis in species such as Vibrio cholorae and that flagella are required for infectivity in species such as Helicobacter pylori.[82] Intracellular gel-forming mucins are stored in a compact and condensed form in granules within mucus-secreting cells. They are stored in solution with a high concentration of calcium ions and protons which is thought to be necessary to mask the anionic charge and prevent electrostatic repulsion, upon secretion mucins expand 1000-3000 fold taking up water to form a gel as

calcium is exchanged for sodium and the pH rises.[79] One consequence of mucins being stored in such a compact form is that when they're released they can obstruct the airway which in mouse models appears necessary for the clearance of helminth infection[83] and may provide a clue to their evolution.

Normal human airway mucus is a hydrogel composed of approximately 98% water, 0.9% salt, 0.8% globular proteins, and 0.3% high-molecular-weight mucin polymers.[84] Mucin hypersecretion may increase the concentration of solids up to 15% resulting in viscous elastic mucus that is not easily cleared.[85] 17 genes encode mucins in the human genome of which the gene products of seven are secreted and the remainder are membrane bound. Five of the secreted mucins have terminal cysteine rich domains that can form disulfide bonds resulting in polymers that impart the properties of a gel. MUC5AC and MUC5B, two secreted gel-forming mucins, are strongly expressed in the human respiratory tract. MUC5AC is predominantly expressed in the conducting airways and MUC5B is predominantly expressed in the respiratory airways (muc5b is also expressed in salivary glands, cervix, gallbladder, seminal fluid, and middle ear epithelium). Secreted mucins are large glycoproteins (up to 3x10^6 D per monomer), ranking among the largest molecules encoded in mammalian genomes, and their expression induces and requires an endoplasmic reticulum stress response.[86] Mucin production and secretion are regulated by distinct mechanisms. Production is highly regulated at transcriptional level. The ErbB family of proteins contains four receptor tyrosine kinases, structurally related to the epidermal growth factor receptor (EGFR), its first discovered member. ErbB-receptor signaling appears important for MUC5AC production since inhibition blocks MUC5AC up-regulation by diverse stimuli. Interleukin-13 (IL-13) is a cytokine secreted by T helper type 2 (Th2) cells, CD4 cells, Natural killer T cell, Mast cell, Basophil cells, Eosinophil cells and Nuocyte cells. IL-13 is a central regulator in IgE synthesis, goblet cell hyperplasia, mucus hypersecretion, airway hyperresponsiveness, fibrosis and chitinase up-regulation. It is a mediator of allergic inflammation and different diseases including asthma. IL-13 appears important because it increases MUC5AC expression (IL-1 beta appears to be an important stimulus for MUC5b expression[83]).

Basal levels of production and secretion of MUC5AC and MUC5B change as part of an allergic response. The production of MUC5AC can increase 40-200 times as high as normal levels in humans with similar findings in mice, MUC5B increases more modestly, 3 to 10 times in mice. The most important stimulus for secretion appears to be ATP which acts on apical membrane purinergenic ($P2Y_2$) receptors. Once secreted mucus gel is propelled in a proximal direction towards the mouth, by ciliary beating as part of the mucociliary escalator, where is expectorated or swallowed. [85]

5.1.2 MUC5B rs3570950 and respiratory disease

Expression and localisation of MUC5AC and MUC5B is different in patients with lung disease compared with health controls. MUC5AC expression is increased in asthma for example, while MUC5B expression is increased in COPD[87] and IPF. In COPD MUC5b expression occurs in more proximal airways, whereas in IPF it localised to the bronchiole.[88] MUC5b appears to be particularly important in IPF.

The gain of function promoter variant rs5270590, 3.5 kb upstream of the mucin 5b (MUC5B) transcriptional start site, is the strongest identified risk factor (genetic or otherwise) for the development of either sporadic or familial IPF. The largest study to date (1616 non-hispanic white patients with fibrotic interstitial pneumonias and 4683 controls) estimated that the odds of developing pulmonary fibrosis for those with one copy of the risk allele were 4.5 times (95% CI: 3.9, 5.2) the odds of those with no copies and that the odds for those with two copies are 20.2 times those with no copies (95% CI: 15.2–27.0).[89] The strength of association is substantially higher than for most other common risk variants for complex disease with the exception of the human leukocyte antigen (HLA) region for some autoimmune diseases such as type-1 diabetes mellitus and systemic lupus erythmatosis which have OR greater than 10. The association between rs35705950 has been replicated in 3 genome wide association studies (GWAS) and a total of 10 independent cohorts including a Mexican cohort and two Asian cohorts and is thought to account for about a third of IPF cases.[90] However, penetrance is low with up to 20% of non-Hispanic whites having a least one copy of the variant yet

IPF occurring only rarely. The rs35705950 variant is a G-to-T transversion that occurs in an area of the MUC5B 5' flanking region, a region which has characteristics of being an enhancer subject to epigenetic control via DNA methylation and histone modification.[88] An enhancer is a sequence of DNA that functions to enhance transcription. A promoter is a sequence of DNA that initiates the process of transcription. A promoter has to be close to the gene that is being transcribed while an enhancer does not need to be close to the gene of interest. Publicly available data through the Encyclopedia of DNA Elements (ENCODE) suggest MUC5b promoter site is a complex area of the genome with many transcriptional factors showing evidence of binding.[91] In other words MUC5b expression likely a function of genetic and non-genetic factors.[90] In addition to IPF, rs35705950 has been found to be positively associated with interstitial lung abnormalities (ILA), chronic hypersensitivity pneumonitis (CHP), rheumatoid arthritis associated interstitial lung disease (RA-ILD), and myeloperoxidase-antineutrophil cytoplasmic antibody-associated vasculitis associated interstitial lung disease (AAV-ILD).[92] It has also been found to not be associated with cutaenous systemic sclerois interstital lung disease (SSc-ILD), sarcoidosis, and myositis-ILD. [93]

5.1.2.1 Potential role in IPF pathogenesis (and normal function inc make the point penetrance low need something else too e.g occ exposure and bring in recent review and coal dust)

The rs5270590 variant is associated with a 34 fold increase in expression of MUC5b compared with wild type in healthy control populations and a 5 fold increase in patients with IPF (see figure 1).[90] In IPF patients distal airway MUC5b is expressed preferentially, compared with MUC5Ac. MUC5b also expressed in honeycomb cysts, a defining characteristic of the usual interstitial pneumonia CT pattern typically seen in IPF.[94]

Proposed mechanisms for the role of the rs5270590 variant in the pathogenesis of IPF include:

1. excessive production of MUC5B by stem cells that attempt to regenerate injured bronchiolar and alvelar epithelium could disrupt normal development pathways and highjack normal reparative mechanisms of the distal lung resulting in fibroprolferation and honeycomb cyst formation.
2. excessive MUC5B production leads to reduced mucociliary function, retention of particles, and enhanced lung injury.
3. interaction between MUC5b and motile cilia since distinct cilium gene expression in IPF lung has been observed.
4. excessive MUC5b production inducing endoplasmic reticulum stress and the unfolded protein response.[90]

Muc5b has been studied in mice. A Mub5b knockout mouse study found that muc5b is essential for mucociliary clearance, for controlling airway and middle ear infections, and maintaining immune homeostasis in the lungs. Knockout mice had airflow limitation and died from infection by multiple bacterial species, including Staphylococcus aureus.[95] A transgenic muc5b mouse model of muc5b overexpression found that overexpression causes mucociliary dysfuction and enhances lung fibrosis on response to bleomycin.[96] Intriguingly, in recent bleomycin lung fibrosis model studies lung fibrosis was attenuated and mortality reduced in both germ-free mice and IL-17B deficient mice supporting the concept that fibrosis in response to epithelial injury is mediated by interaction of the immune system with microbiota.[97][98]

5.1.3 INFECTION/IMMUNITY

The frequency of the disease associated allele at rs35705950 exceeds 10% in European populations (https://www.ncbi.nlm.nih.gov/snp/rs35705950) but is less than 1% in African and East Asian populations. Clearly the rs35705950 variant is not subject to negative selection due to IPF risk since onset is well after the reproductive age begins[90]; the variation in frequency observed is consistent with strong positive selection. The increased MUC5b expression in the airways associated with the rs35705950 variant may have conferred a survival advantage by providing protection

against lung infection. [86][83] A relation between the rs35705950 variant, disease risk, and infection is also supported by the observation that in a prospective study of 65 IPF patients have higher bacterial loads than COPD and healthy controls and within IPF patients those with homozygous (TT) for variant had significantly lower bacterial loads (P=0.01), measured by 16S rRNA quantitative polymerase chain reaction of bronchoalveolar lavage samples. Within IPF those with higher bacterial loads were also at increased risk of death.[99] These finding are consistent with observation that the rs35705950 variant is associated with improved survival in IPF[100] and fewer acute respiratory disease events in the COPDGene cohort with interstitial features.[101] However, these studies are vulnerable to index event bias, by which selection of subjects according to disease status creates biased associations if common causes of incidence and prognosis if not properly accounted for.[102] For example, it is known that the rs35705950 variant is associated with interstitial lung abnormalities[103], since the diagnosis of IPF relies heavily on radiological appearances individuals with the variant might tend to be diagnosed earlier in the course of their disease giving the false impression, when comparing them to IPF patients without the disease variant that is associated with survival. Further support for the importance of infection in IPF provided by the observation that immunomodulatory therapies such as interferon gamma, ethanercept, prednisolone, azathioprine and N-acetylcysteine have failed to prolong survival in IPF[104] to prolong survival in IPF, from a small (N = 181) double blinded randomized controlled study which found reduced symptom burden and improved survival associated with cotrimoxazole[105], as well as evidence from genetic and animal studies. IPF GWAS have identified single nucleotide variants associated with disease susceptibility in the Toll interacting protein (TOLLIP) gene, for example rs111521887. TOLLIP is an inhibitory adaptor protein within Toll-like receptors (TLR) and part of the innate immune system recognising pathogen associated molecular patterns (PAMPs)[106] and, intriguingly, in a mouse bleomycin lung fibrosis model the absence of a microbiome protected against mortality.[97]

5.1.4 INORGANIC OCCUPATIONAL STIMULI

While the frequency of the disease associated allele at rs35705950 exceeds 10% in European populations(https://www.ncbi.nlm.nih.gov/snp/rs35705950), its penetrance is low. The median prevalence of IPF for men and women in Europe is approximately 3.75 per 100000 for the period 2001-2013[107], other genetic and/or environmental factors must be at play. In addition to responding to PAMPs as outlined above the innate immune system also responds to damage-associated molecular patterns (DAMPs) which can result from inhalation of inorganic respirable toxins such as silica or asbestos.[108] Secretion of the inflammatory cytokine IL-1beta (which is also a stimulus for MUC5b expression) is elevated in alveolar macrophages of patients with ILD, including IPF, sarcoidosis, silicosis, RA-ILD, and asbestosis.[109][110] Inflammasome are multiprotein intracellular complexes that detect pathogenic microorganisms (PAMPs) and sterile stressors (DAMPs). The NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome is an intracellular sensor that detects a broad range of PAMPs and DAMPs leading to caspase 1-dependent release of the pro-inflammatory cytokines IL-1 beta and IL-18, as well as to gasdermin D-mediated pyroptotic cell death.[111] Interestingly the NLRP3 inflammasome appears to be implicated, albeit with differing activation patterns[112], in all of these conditions, interaction between smoking (a risk factor for IPF) and the NLRP3 inflammasome is recognised, and recent work has shown age-dependent susceptibility to pulmonary fibrosis in a bleomycin-induced lung injury mouse model.[113] Occupational risk factors such as metal, wood, and stone dust exposure are well recognised in IPF, accounting for up to 8% of cases the basis of a meta-analysis of case-control data[114] and its likely that innate immune system activation via the NLRP3 inflammasome and other means by occupational exposures mediates this risk.

5.2 Conclusion

The apparently complex interplay between exposure to organic and inorganic respiratory toxins, the mucus barrier, respiratory epithelium and resident

cells such as alveolar macrophages in idiopathic pulmonary fibrosis remains incompletely characterised but genetic, epigenetic, gene-expression, and epidemiological studies are beginning to fill in the gaps. Gene-environment interaction between the rs5270590 variant and occupational inorganic respiratory toxins such as asbestos may modulate IPF risk and help to explain the incomplete penetrance observed. Studies to date which have selected patients on the basis of a diagnosis of IPF and then stratified by MUC5b genotype are at risk of index-event bias. A large case-control study of IPF which captures details of occupational exposures, genotype, and potential confounders, whilst also measuring factors likely to affect disease pickup such as disease severity and radiographic changes is required.

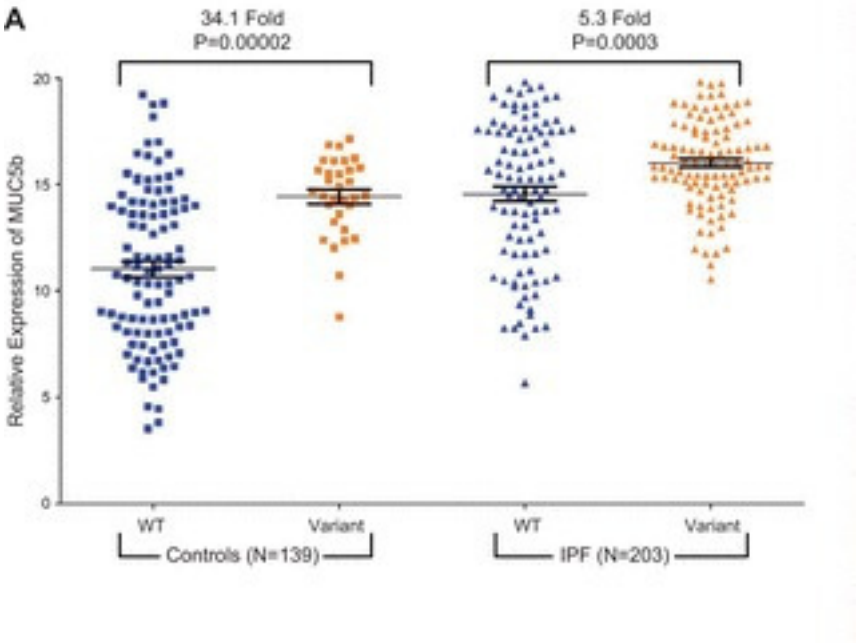

Figure 5.1: MUC5b expression (Evans 2016)

Chapter 6

Idiopathic pulmonary fibrosis job exposures study (IPFJES): Is occupational asbestos exposure an under-regcognised cause of IPF?

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[115]; they will be identified monthly by the MDT coordinator of participating centres.[116]

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[40] 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 $\alpha = 0.05$[117]; my planned sample size sample size includes a margin for model stability and incomplete data.[118]

Secondary (exploratory) analysis will investigate gene-environment interaction. The global minor allele frequency of MUC5B rs35705950 is 0.05.[119] With an estimated prevalence of IPF of 20/100000[1] and with ORs 2.0 for asbestos exposure and 6.8 for rs35705950[120], 113 cases would be required to detect a minimum interaction OR of 4.0.[121] 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

Genotyping

Genotypes of the MUC5B SNP rs35705950 were determined using TaqMan assays (Life Technologies, Carlsbad, CA). Reactions were performed in 384-well plates, and fluorescence was read using an Applied Biosystems Viia7 Sequence Detection System.

In tincidunt viverra dolor, ac pharetra tellus faucibus eget. Pellentesque tempor a enim nec venenatis. Morbi blandit magna imperdiet posuere auctor. Maecenas in maximus est.

6.3 Results

These are the results. Curabitur vulputate nisl non ante tincidunt tempor. Aenean porta nisi quam, sed ornare urna congue sed. Curabitur in sapien justo. Quisque pulvinar ullamcorper metus, eu varius mauris pellentesque et. In hac habitasse platea dictumst. Pellentesque nec porttitor libero. Duis et magna a massa lacinia cursus.

6.4 Discussion

possibility of missed chronic HP [122]

6.5 Conclusion

This is the conclusion to the chapter. Nulla sed condimentum lectus. Duis sed tempor erat, at cursus lacus. Nam vitae tempus arcu, id vestibulum sapien. Cum sociis natoque penatibus et magnis dis parturient montes, nascetur ridiculus mus.

Chapter 7

Conclusion

7.1 Thesis summary

In summary, pellentesque habitant morbi tristique senectus et netus et malesuada fames ac turpis egestas. Nunc eleifend, ex a luctus porttitor, felis ex suscipit tellus, ut sollicitudin sapien purus in libero. Nulla blandit eget urna vel tempus. Praesent fringilla dui sapien, sit amet egestas leo sollicitudin at.

7.2 Future work

chronic hp

Appendix 1: IPF epidemiology code

IPF epidemiology

Appendix 2: IPFJES study documentation

IPFJES study documentation

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