IPF JES

Idiopathic Pulmonary Fibrosis Job Exposures Study

A case-control study to investigate whether occupational asbestos exposure is an under-recognized cause of idiopathic pulmonary fibrosis (IPF) using an interview to measure previous asbestos exposure and a blood test to investigate genetic susceptibility.

Version 0.4
July 11, 2017

Protocol authorised by:

Name & Role	Date	Signature
Carl Reynolds, Chief Investigator	July 11, 2017	

Study management group

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Clinical Queries

Clinical queries should be directed to Dr Carl Reynolds who will direct the query to the appropriate person.

Sponsor

Imperial College London is the main research Sponsor for this study. For further information regarding the sponsorship conditions, please contact the Head of Regulatory Compliance at:

Joint Research Compliance Office
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This protocol describes the Idiopathic Pulmonary Fibrosis Job Exposures Study (IPF JES) and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study. Problems relating to this study should be referred, in the first instance, to the Chief Investigator. This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

Contents

Key words

Idiopathic pulmonary fibrosis, asbestos, case-control study

Study Summary

Title: Idiopathic Pulmonary Fibrosis Job Exposures Study (IPF JES).

Design: Hospital case-control study.

Aim: To characterize and measure asbestos exposure as an occupational determinant of IPF.

Outcome measures: 1. Association between asbestos exposure and IPF estimated using logistic regression for any vs no asbestos exposure and categories of cumulative exposure and adjusting for age and smoking status. 2. Gene-environment interaction (for MUC5B rs35705950 and asbestos exposure) odds ratio.

Population: Male patients with a new diagnosis of IPF and age-matched controls who have a new outpatient clinic appointment during the study period.

Eligibility: Meets population definition, able to give informed consent, has never worked outside of the UK.

Duration: Three years.

1   Introduction

1.1   Background

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/Wales. Its incidence, currently around 7.5/100,000 person-years, has increased by 5% pa since 2000.[?] 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).[?][?][?] 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[?], patterns that are not unique to the UK.[?] The prognosis is poor, with a median survival of three years.[?][?]

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.[?] 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'.[?][?][?][?]

Identification of occupational asbestos fibre exposure as an under-recognized 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. Details of how the proposed research will inform government policy and change working practices are provided in Appendix A.

In preparing this protocol, I examined mortality trends in England and Wales for IPF and asbestos-related diseases. UK age-standardized mortality rates from 1974 to 2012 continued to rise with marked sex and regional variations, consistent with occupational exposure being an under-recognized cause of IPF.[?] I analysed European age-standardised mortality rates for mesothelioma and IPF for 27 countries for which data was available and found a positive correlation (r = 0.51, p = 0.007). I collated 13 case-control studies of IPF and occupational dust exposure; eight reported significant associations with metal dust exposure[?][?][?][?][?], four with wood dust[?][?][?] and two with stone dust.[?][?]

Finally, I analysed the limited occupational information in a recent case-control study, designed to examine the role of thrombosis in IPF.[?] Using an approach from a large mesothelioma study based on proportional mortality ratios[?] I estimated the odds ratio (OR) associated with ever having had a job with probable asbestos exposure was 2.8 (95% CI: 1.42-5.75, p = 0.001) adding further weight to the argument that occupational asbestos exposure in IPF should be properly investigated. Supplementary figures and a table of previous case-control studies are provided in Appendix B.

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[?][?][?], a group who are

frequently exposed to dust containing asbestos fibres[?] and who in a recent UK study, had the highest risk of mesothelioma.[?] 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.[?][?][?][?][?] This allows too the examination of 'exposure-response' relationships, entirely lacking in the published literature.

Second, all but two studies[?][?] used community controls. While this is generally desirable, hospital controls are preferred in circumstances when acceptable community control participation rates cannot be achieved, case acquisition is incomplete, or recall bias is an issue. Recent participation rates for community controls in UK studies of IPF have been as low as 28%;[?] and a recent US series estimated that the ante-mortem diagnosis of IPF was missed in 20% of cases.[?] Further, the use of community controls for hospital cases risks significant information mismatch on exposures. While hospital controls are less representative of the base population, their use does not prevent a study from being either scientifically valid or generalizable[?] as is well demonstrated by a recent influential UK hospital case-control study which found that exposure to metal fume predisposed to infectious pneumonia.[?]

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

I propose a new case-control study that systematically collects lifetime occupational histories to derive exposure risk using formal asbestos exposure assessment. I will also collect IPF susceptibility genotypes to permit me, uniquely, to examine exposure-response relationships, latency periods and genotype-exposure interactions.

2   Study 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?

3   Study design

3.1   Study outcome measures

Primary outcome   Association between asbestos exposure and IPF estimated using logistic regression for any vs no asbestos exposure and categories of cumulative exposure and adjusting for age and smoking status.

Secondary outcome   Gene-environment interaction odds ratio (for MUC5B rs35705950 and asbestos exposure)

4   Participant entry

4.1   Pre-registration evaluations

Pre-registration evaluation will include screening for eligibility using inclusion and exclusion criteria.

4.2   Sampling

Cases and controls will be frequency matched on age categories.

4.3   Inclusion criteria

- Cases

    - Male
    - New diagnosis of IPF between February 2017 and October 2019

- Controls

    - Male
    - New outpatient department attendee between February 2017 and October 2019

4.4   Exclusion criteria

- Cases

    - Unable to give informed consent
    - Ever worked outside of the UK

- Controls

    - Unable to give informed consent
    - Ever worked outside of the UK

4.5   Withdrawal criteria

Research participants will be withdrawn from the study upon their request or if for any reason they are unable to complete the study interview.

5 Adverse events

5.1 Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical study subject.

Serious Adverse Event (SAE): any untoward and unexpected medical occurrence or effect that:

- Is life-threatening refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe

- Requires hospitalisation, or prolongation of existing inpatients hospitalisation

- Results in persistent or significant disability or incapacity

- Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

5.2 Reporting Procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the Chief Investigator in the first instance.

5.2.1 Non serious AEs

An SAE form should be completed and emailed to the Chief Investigator within 24 hours. However, relapse and death due to IPF, and hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

All SAEs should be reported to the Imperial College London where in the opinion of the Chief Investigator, the event was:

- related, ie resulted from the administration of any of the research procedures; and

- unexpected, ie an event that is not listed in the protocol as an expected occurrence

Reports of related and unexpected SAEs should be submitted within 15 days of the Chief Investigator becoming aware of the event, using the NRES SAE form for non-IMP studies. The Chief Investigator must also notify the Sponsor of all SAEs.

Local investigators should report any SAEs as required by their Local Research Ethics Committee, Sponsor and/or Research & Development Office.

6 Assessment and follow up

Research participants will complete an interview and a blood test. The study will end when analysis of the last research participant is complete.

7 Statistics and data analysis

For the primary analysis 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 indicate that the probability of exposure among controls is 0.63. If the true OR for disease in exposed subjects relative to unexposed subjects is 1.5, I will need to recruit 460 case patients and 460 control patients to be able to reject the null hypothesis that this odds ratio equals 1 with $\beta = 0.2$ and $\alpha = 0.05$; my planned sample size includes a margin for model stability and incomplete data.

Secondary (exploratory) analysis will investigate gene-environment interaction. The global minor allele frequency of MUC5B rs35705950 is 0.05. With an estimated prevalence of IPF of 20/100000 and with ORs 1.5 for asbestos exposure and 6.8 for rs35705950, 460 cases would be required to detect a minimum interaction OR of 5.0.

8 Regulatory issues

8.1 Ethics approval

The Chief Investigator has obtained approval from the Research Ethics Committee via IRAS. The study must be submitted for Site Specific Assessment (SSA) at each participating NHS Trust. The Chief Investigator will require a copy of the Trust R&D approval letter before accepting participants into the study. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions.

8.2 Consent

Consent to enter the study will be sought from each participant only after a full explanation has been given, an information leaflet offered, and time allowed for consideration. Signed participant consent will be obtained. The right of the participant to refuse to participate without giving reasons will be respected. In these cases the participant will be withdrawn from the study and their data and samples destroyed. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3 Confidentiality

The Chief Investigator will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act.

8.4 Indemnity

Imperial College London holds negligent harm and non-negligent harm insurance policies which apply to this study.

8.5 Sponsor

Imperial College London will act as the main Sponsor for this study. Delegated responsibilities will be assigned to the NHS trusts taking part in this study.

8.6 Funding

The Wellcome Trust are funding the research.

8.7 Audits and inspections

The study may be subject to inspection and audit by Imperial College London under their remit as sponsor and other regulatory bodies to ensure adherence to GCP and the NHS Research Governance Framework for Health and Social Care (2nd edition).

9 Study management

The day-to-day management of the study will be co-ordinated through Dr Carl Reynolds.

10 Publication policy

All research findings will be published in accordance with the Wellcome Trust and Imperial College London open access publication policies.

Appendix A   Research outputs

There will be three main outputs of the study:

1. Data from the study, including anonymised raw data, will be communicated to the wider academic community, and policy-makers, by publication and presentation at national and international respiratory and epidemiology meetings.

2. Data from the study will inform HSE and policy decisions with respect to work place dust control; we are collaborating with Andrew Darnton who works at HSE specialising in mesothelioma and other asbestos related diseases.

3. Data from the study will inform policy decisions with respect to the use of anti-fibrotic treatments in patients with asbestosis. We will establish good working relations with NICE and the NHS England Specialist Respiratory Clinical Reference Group to communicate our findings. NHS patients with IPF due to occult occupational asbestos exposure may be entitled to compensation and our work may lead to reconsideration of current restrictions on disease modifying anti-fibrotic therapies for patients with asbestosis.

An estimated 125 million people around the world work in environments in which they are exposed to asbestos, and at least 107,000 people die from occupational exposure to asbestos every year[?] . Understanding the role of asbestos exposure in idiopathic pulmonary fibrosis is an important data point for disease prevention policy measures.