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Occupational exposure and severe pulmonary fibrosis

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Summary
Background: External agents, especially metal and wood dust, are believed to be risk factors for development of idiopathic pulmonary fibrosis (IPF). The aim of this case–control study was to investigate which occupational exposure types are associated with development of severe pulmonary fibrosis (PF), and especially IPF.
Methods: An extensive postal questionnaire including 30 specific items regarding occupational exposure was completed by 181 patients with severe PF and respiratory failure reported to the Swedish Oxygen Register, among whom 140 were judged as having IPF. The questionnaire was also completed by 757 control subjects. We stratified data for age, sex and smoking and calculated odds ratios (ORs).
Results: We found increased risk for IPF in men with exposure to birch dust (OR 2.7, 95% confidence interval (95% CI) 1.30–5.65) and hardwood dust (OR 2.7, 95% CI 1.14–6.52). Men also had slightly increased ORs associated with birds. We did not find any increased risk in association with metal dust exposure.
Conclusion: Exposure for birch and hardwood dust may contribute to the risk for IPF in men.
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Introduction

Pulmonary fibrosis (PF) and in particular idiopathic pulmonary fibrosis (IPF) is increasing as a cause of death in the Western world.[1–3] In Sweden PF, mainly IPF, has increased as

a cause of chronic hypoxemia treated with long-term oxygen therapy (LTOT).[4]

The cause of IPF, the most common of the idiopathic interstitial pneumonias,[5] is multi-factorial and includes external factors.[6] A mineralogical micro-analysis of lung tissue from IPF patients showed deposits of silica/silicate,[7] and mineral dusts have been found to directly induce fibrosis in the airway wall.[8] Five case–control studies have demonstrated increased occupational risk for IPF,[9–13] especially with exposure to metal dust, although not supported by a study on standardised mortality ratios.[14] In three of these studies, wood dust exposure was increased among the IPF cases.[9–11] The association between IPF and metal was further confirmed in a case–control study nested in an occupational cohort.[15] Farming,[9,10,12] stone or sand dust[11,12] as well as smoking[16] also seem to be risk factors for IPF. Most studies are from the US, UK or Japan, and there is a lack of studies from northern Europe, where exposure to soft wood and metals for instance may be more frequent.

Hence, we have performed a case–control study on a national sample of patients diagnosed with PF and starting LTOT. The specific aim of the study was to further elucidate types of occupational exposure that increase the risk for this lethal disease, with the long-term intention to prevent new cases.

Materials and methods

The Swedish Oxygen Register was started in 1987 with the purpose of assessing quality of LTOT in Sweden in terms of access to therapy, adherence to national guidelines and performance.[17]

The cases in the present study were recruited from the patients with chronic hypoxemia caused by PF, and came from 23 out of 29 general hospitals in Sweden covering 88% of the population in Sweden. All registered patients ($n = 241$) receiving LTOT between 1 February 1997 and 4 April 2000 were included as cases. In the subsequent analysis, the cases were divided into two groups, viz. all cases (the PF sample), and a restricted sample of cases (the IPF sample), from which all subjects with known aetiology of their fibrosis were excluded.

As controls we selected a random sample ($n = 1000$) from the general population of Sweden with the same age range as the cases (Fig. 1).

Cases and controls received an extensive postal questionnaire with items about their occupation, specific occupational exposure, drugs used and smoking habits. The questionnaire and wording of the items have been described elsewhere.[18]

The classification of the subjects' occupational exposure was based upon their self-reports. The questions about occupational exposure were worded as follows: "In your work, have you ever been exposed to ...?". Such items covered 29 different types of occupational exposure.

The questionnaire was completed by 193 PF patients (cases). Twelve were excluded due to erroneous diagnosis in the Oxygen Register. Hence, 181 subjects were included in the PF sample. From this sample, we excluded 27 subjects because of rheumatoid arthritis ($n = 14$), scleroderma ($n = 4$), Sjögren's syndrome ($n = 2$) and other diseases such
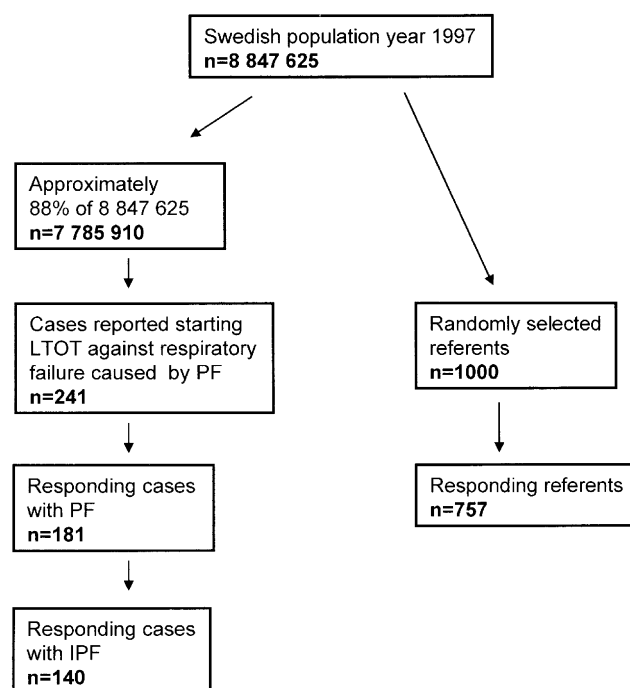
Figure 1 Flow chart showing the selection of cases and referents for the study. IPF: idiopathic pulmonary fibrosis; LTOT: long-term oxygen therapy; PF: pulmonary fibrosis.

as systemic sclerosis and systemic lupus erythematosus ($n = 7$). An additional 14 cases were excluded because of known aetiology, viz. asbestosis ($n = 6$), silicosis ($n = 5$), and irradiation or drug-induced PF ($n = 3$). Hence, 140 cases were included in the IPF sample.

The data from the Oxygen Register and the questionnaires did not allow verification of IPF according to accepted major and minor criteria.[19] When identifying the IPF patients we therefore excluded all patients with host susceptibility or known external agents. We then assumed that the remaining patients had IPF, being the largest group of the idiopathic interstitial pneumonias and serious enough to cause chronic respiratory failure.

Of the 1000 controls being sent the questionnaire, 757 responded. Table 1 shows baseline data for the cases and controls with regard to age and smoking status.

Every regional ethics committee in Sweden, the National Board of Health and Welfare and the Data Inspection Board approved the study. All patients and controls gave their informed consent.

Statistical analyses

For all analyses, the Statistical Analysis System (SAS) statistical package, version 8.1 (SAS Institute, Inc., Cary, NC, US), was used. The cases and controls were divided into the following three groups according to year of birth: 1906–1923, 1924–1936 and 1937–1969. The cases were diagnosed in the years 1968–1999, and they were further divided into three groups according to their year of diagnosis, as follows: 1968–1986 (41%), 1987–1993 (28%) and 1994–1999 (31%).

Relevant exposure was exposure that had occurred before the onset of PF, approximated as the year of diagnosis. It was also necessary to define an anchor point in time for each control. Hence, in each birth year group, the controls were randomly assigned to a year of diagnosis group. The number of controls allocated to each year of diagnosis group was weighted by the number of actual cases. Each control was then assigned the mid-year in his or her year of diagnosis group as its anchor year.

To be classified as exposed, subjects had to report exposure 5 years or more before diagnosis. This means that exposure occurring during the 5-year period preceding the diagnosis was not included in the analysis. In the final analysis, the exposures were merged into five categories: occupational exposure, organic dust, wood dust, inorganic dust, and metal dust.

Two groups of cases were analysed, the whole group of cases (the PF sample) and the restricted sample (the IPF sample). The cases and controls were stratified for sex, age group and birth year group, and odds ratios (ORs) were calculated according to Mantel–Haenszel. Only exposure categories with five or more exposed cases were considered in the final analysis. Ninety-five per cent confidence intervals (95% CIs) were calculated with the test-based method.[20] Logistic regression modelling was also used to adjust for overlapping exposures, and ORs with 95% CIs were estimated.

Results

Subjects with any occupational exposure had an increased risk for PF (OR 1.6, 95% CI 1.06–2.37), but not for IPF (Table 2). Exposure to wood dust increased the risk for PF (OR 1.7, 95% CI 1.03–2.95).

When stratifying the analyses according to sex, we observed the highest risks for PF among men (Table 2). Exposure to wood dust among men doubled the risk for PF (OR 2.1, 95% CI 1.18–3.65).

In Table 3, the risks for all the exposures are shown for PF and IPF, and in men and women together. The analyses were restricted to exposures affecting five or more cases. An increased risk for PF was associated with exposure to mineral dust, birds, flour dust, dust from fur or fir, birch dust, hardwood dust and fire fumes. In cases with IPF, the exposures with increased risk were only birch dust (OR 2.4, 95% CI 1.18–4.92) and hardwood dust (OR 2.5, 95% CI 1.06–5.89). The OR for flour dust and IPF was just below the significance level (OR 1.9, 95% CI 0.98–3.74).

When separately analysing men and women with five or more exposed subjects to a group, risks remained increased for IPF in men exposed to birch dust (OR 2.7, 95% CI 1.30–5.65) and hardwood dust (OR 2.7, 95% CI 1.14–6.52). Men also had an increased OR associated with birds (OR 2.7, 95% CI 1.00–7.06) (not shown in the table). There was no increased risk for any of the detailed exposures in the women.

There were 10 PF cases reporting occupational exposure to hardwood dust. In the questionnaire, there was also information about occupations. Their longest held occupation was wood-products machine operator, forester, cabinet-makers, machine operator, telephone servicers and a blacksmith. There were also two carpenters and two subjects not reporting their occupation.

We also analysed the material using a latency period of 10 years instead of 5 years with similar results. The same exposures were associated with increased risks,

Table 1 Description of the study population (the cases were the subjects in the pulmonary fibrosis sample*.

	Men		Women	
	Cases (*n* = 114)	Referents (*n* = 349)	Cases (*n* = 67)	Referents (*n* = 408)
Age (years)	74.4	64.2	72.0	63.4
Never-smokers (%)	15.7	38.7	54.5	52.6
Ex-smokers (%)	80.6	46.2	43.8	27.4
Current smokers (%)	3.7	15.1	1.7	20.0

*The IPF sample (*n* = 140) was included in the PF sample (*n* = 181).

Table 2 Odds ratio* according to occupational exposure, for the pulmonary fibrosis sample and the idiopathic pulmonary fibrosis sample, stratified by sex, year of diagnosis, birth year and smoking, and for the pulmonary fibrosis sample divided into men and women, stratified by year of diagnosis, birth year and smoking.

	PF sample (*n* = 181)			IPF sample (*n* = 140)			Men with PF (*n* = 114)			Women with PF (*n* = 67)		
	n[†]	OR	95% CI	*n*[†]	OR	95% CI	*n*[†]	OR	95% CI	*n*[†]	OR	95% CI
Any occupational exposure	123	1.6	1.06–2.37	86	1.1	0.71–1.72	89	1.7	0.95–3.12	34	1.5	0.84–2.55
Organic dust	69	1.4	0.98–2.12	49	1.1	0.74–1.76	54	1.7	1.04–2.70	15	1.1	0.56–2.10
Wood dust	34	1.7	1.03–2.95	22	1.2	0.65–2.23	33	2.1	1.18–3.65	–	n.a.	–
Inorganic dust	57	1.2	0.79–1.97	35	0.9	0.53–1.49	54	1.4	0.84–2.23	–	n.a.	–
Metal dust	37	1.0	0.62–1.69	25	0.9	0.51–1.59	34	1.1	0.62–1.79	–	n.a.	–

*Determined using Mantel–Haenszel. Note that only exposures with 10 or more exposed cases were considered. PF: pulmonary fibrosis; IPF: idiopathic pulmonary fibrosis; 95% CI: 95% confidence interval; n.a.: not applicable.
[†]*n*: number of exposed cases; OR: odds ratio.

Table 3 Odds ratio* for the pulmonary fibrosis sample and the idiopathic pulmonary fibrosis sample according to occupational exposure, stratified by sex. Number of controls exposed for each occupational exposure, divided into men and women.

Exposure	PF (n = 181)			IPF (n = 140)			Controls, men (n = 349)	Controls, women (n = 408)
	$n^\dagger$	OR	95% CI	$n^\dagger$	OR	95% CI	$n^\dagger$	$n^\dagger$
Welding fumes	24	1.1	0.64–1.78	15	0.8	0.42–1.42	70	1
Grinding, polishing, milling or turning or other processing of metals	22	1.0	0.57–1.64	15	0.8	0.43–1.44	62	13
Soldering	13	0.9	0.47–1.65	9	0.7	0.31–1.38	44	8
Blasting	7	3.2	1.10–9.32	–	n.a.	–	7	0
Mineral dust	27	2.4	1.39–4.06	14	1.4	0.74–2.72	39	2
Coal dust or graphite dust	11	1.8	0.83–3.82	9	1.8	0.80–4.07	18	3
Artificial mineral fibres	22	1.2	0.67–2.00	14	0.8	0.45–1.57	60	4
Asbestos	26	1.2	0.72–2.00	15	0.8	0.44–1.47	66	6
Birds	16	2.3	1.22–4.34	10	1.7	0.82–3.62	11	22
Mouldy hay or straw	12	1.4	0.68–2.68	8	1.1	0.50–2.48	23	10
Grain dust	17	1.3	0.70–2.21	12	1.1	0.57–2.15	32	22
Flour dust	18	2.1	1.14–3.76	13	1.9	0.98–3.74	19	18
Fur or fir dust	32	2.1	1.31–3.47	20	1.4	0.82–2.52	48	9
Birch dust	16	2.6	1.32–5.18	13	2.4	1.18–4.92	18	4
Hardwood dust	10	2.4	1.05–5.69	9	2.5	1.06–5.89	12	2
Paper dust	9	1.3	0.60–2.91	6	1.1	0.43–2.70	17	8
Textile dust	13	1.4	0.74–2.72	10	1.3	0.64–2.70	12	33
Radiation	6	0.9	0.36–2.28	5	0.9	0.32–2.28	16	8
Solvents	28	1.3	0.79–2.05	19	1.0	0.60–1.77	64	14
Fire fumes	8	2.9	1.10–7.58	5	2.3	0.74–6.97	9	0
Engine exhausts	24	0.9	0.54–1.50	15	0.7	0.39–1.27	74	11
Irritating gases (ammonia, chlorine dioxide, chlorine gas, sulphur dioxide)	13	1.5	0.79–3.00	10	1.5	0.71–3.06	22	10
Environmental tobacco smoke	53	1.0	0.71–1.45	40	0.9	0.61–1.36	117	90
Cutting oils/fluids	8	1.0	0.43–2.23	5	0.8	0.28–2.01	25	0
Rapid glues (Loctite®, cyanoacrylates or Omnifit®)	6	1.0	0.37–2.45	6	1.9	0.38–2.37	18	2

*Determined using Mantel–Haenszel. Note that the exposure categories are not mutually exclusive. Only exposures with five or more exposed cases were considered. IPF: idiopathic pulmonary fibrosis; PF: pulmonary fibrosis; 95% CI: 95% confidence interval; n.a.: not applicable.

†n: number of exposed cases and controls respectively; OR: odds ratio.

Table 4 Logistic regression models for the pulmonary fibrosis sample giving odds ratios (and 95% confidence intervals) adjusted for sex, smoking, year of birth and year of diagnosis.

Predictor	PF		
	All (n = 181)	Women	Men
Inorganic dust	1.1 (0.70–1.68)	0.55 (0.12–2.53)	1.1 (0.70–1.83)
Organic dust	1.5 (1.00–2.15)	1.2 (0.60–2.22)	1.7 (1.06–2.8)
Metal dust	0.98 (0.61–1.58)	0.82 (0.17–3.82)	0.97 (0.58–1.63)
Wood dust	1.9 (1.12–3.15)	0.50 (0.06–4.11)	2.1 (1.22–3.75)

PF: pulmonary fibrosis.

but the risks were slightly higher. In order to explore a cohort effect, we ran the analyses with the population divided into two groups according to the mean birth year, 1930. We found no clear indication of cohort effect.

We obtained similar results with the logistic regression models (Table 4). Exposure to organic dust (and wood dust) increased the risk for PF, especially among men. When we modelled IPF as the dependent outcome, we found no significant associations.

Discussion

The main findings of this study were increased risks for IPF among men exposed to birch dust and hardwood dust. There were no associations with these exposures in the women, probably because much fewer women work with these materials.

The study included two different samples, PF and IPF subjects. The PF group included all patients with PF reported to the Swedish Oxygen Register. This means that it included patients with different pneumoconiosis and lung fibrosis due to other known diseases. Consequently, exposure to both mineral dust and blasting was associated with increased risk for PF. This broad case selection gives us the opportunity to assess the importance of all types of occupational exposure as risk factors for severe PF. We chose to analyse the risk of occupational exposure not only in the IPF group as previous authors[9–13] but also in the larger sample, since the known aetiology might be only one of several risk factors in those patients.

As a cohort we chose the patients with severe PF in the Swedish Oxygen Register, a national register for assessment of quality of care in LTOT for chronic hypoxemia. In 14% of LTOT patients PF is the responsible disease, but in the whole population of patients with ongoing LTOT only 8–9% have PF. The reason for this discrepancy is higher mortality compared with other patient groups receiving LTOT, such as patients with chronic obstructive pulmonary disease and sequels of pulmonary tuberculosis.[4] The cases included in the present study were around 88% of the Swedish patients with advanced-stage PF as the cause of chronic hypoxemia. According to our findings, the most common cause of severe PF with chronic hypoxemia in Sweden is IPF, which here accounted for 77% of the patients. In 8% known external agents could explain the fibrosis and in another 15% various known host susceptibility factors were found.

In the Swedish Cause of Death Register of the Swedish National Board of Health and Welfare, there is a clear dominance of men in the diagnostic group "other interstitial pneumonias". A large percentage of this group have PF with unknown aetiology. This may indicate a strong relationship with occupational exposure. As previously mentioned, this study was performed in a large part of the Swedish population as a recruitment base, with data from the Oxygen Register of the Swedish Society of Respiratory Medicine.[17] The aim was to investigate whether occupational and environmental exposure is a risk factor in Sweden for severe PF, especially IPF. In the five other case–control studies demonstrating increased occupational risk for IPF, the cases were taken from various selected hospitals[9,11–13] and from a national autopsy register, together with live controls from 12 prefectures.[10]

We chose to use a random sample from the general population of Sweden as the control group rather than using patients from the Swedish Oxygen Register, since the majority of them have chronic obstructive pulmonary disease (COPD). Smoking is the dominating cause of their disease but around 15% of them may have occupational exposure as a risk factor.[21] We would fail to demonstrate the increased risk for pulmonary fibrosis, if the same exposures can increase both the risk of COPD and pulmonary fibrosis.

The exposure assessment in this study was based on self-reporting of certain types of exposure. The exposures were selected because of an *a priori* hypothesis of increased risk for PF. The wording of the items was as specific as possible, and we avoided questions about general classes of substances such as "dust". This probably increased the specificity and decreased the sensitivity of our exposure assessment.[22] Self-reported occupational exposure data could be differentially misclassified by disease status. In a Norwegian study, the sensitivity of the question on exposure to dust and gas was biased by respiratory symptoms but hardly at all by physician-diagnosed asthma.[23] Bias in sensitivity is more important than is bias in specificity for the effect of misclassification of exposure to a common exposure, as in the present study.[24] The details about occupations in the 10 cases exposed to hardwood dust support the validity of self-reported occupational exposure, as there seems to be a relation between occupational title and self-reported exposure.

In the PF sample, there was an increased risk associated with wood dust as a whole, which in contrast to three of the earlier case control studies did not remain when narrowed to IPF, in men and women together.[9–11] However, exposure to dust from birch and hardwood was associated with an increased risk for both PF and IPF in men. The risks were generally high, which probably was an effect of using specific exposure items. Pulmonary fibrosis was also associated with exposure to organic dust, fire fumes, blasting and mineral dust in men. The two latter exposures probably reflect undiagnosed silicosis. Therefore, in Sweden, severe PF appears to be associated with occupational exposure in addition to silica dust. The lack of association between PF, IPF and occupational exposure in women might be due to the fact that few women have had these occupations.

We found, as Harris et al.[14] in a study from death certificates, no association with exposure to metal dust, in contrast to the findings of all other five case–control studies mentioned.[9–13] We can think of three reasons for the difference between our results and those of other investigators. There may be less exposure to hard metal and working environments may be less harmful in Sweden than in the other study populations. There may also be differences in patient selection. In our study, the study population was the whole country, not a specific region, as was the case in two of the other studies.[9,11] In further studies, there is a need for more detailed description of the exposure, methods that have been used in other occupational respiratory epidemiological studies.[25]

In conclusion, exposure to wood dust, especially dust from birch and hardwood, may contribute to the risk for IPF in men.

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