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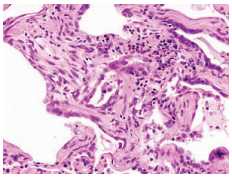

Occupational and Environmental Risk Factors for Idiopathic Pulmonary Fibrosis in Egypt: A Multicenter Case-Control Study

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Abstract

Background: Despite the advances in medical therapy and technology, the prognosis of idiopathic pulmonary fibrosis (IPF) remains poor and the need for disease prevention based on identifying the risk factors becomes mandatory. Occupational and environmental exposures were studied in several countries and found to play important role in the disease development. However, in Egypt, a little attention has been paid to study the effect of these factors in the disease development.

Objective: To identify the occupational and environmental risk factors associated with the development of IPF in Egypt.

Methods: A multicenter hospital-based case-control study was carried out in chest hospitals affiliated to three Egyptian cities—Cairo, Tanta and Mansoura. Subjects were 201 patients with confirmed IPF (cases) and 205 age-, sex- and residence-matched controls. Data on occupational and environmental factors were obtained from a questionnaire. Multiple logistic regression analysis was used to determine the independent risk factors of IPF in both sexes for single factors with adjustment for age, residence and smoking status.

Results: Compared with the controls, the risk of IPF in male workers was observed to increase significantly in chemical and petrochemical industries and carpentry and wood working (OR=2.56, 95% CI: 1.02–7.01), and with occupational exposures to wood dust and wood preservatives. Among female workers, a significant increase was observed in farming (OR=3.34, 95% CI: 1.17–10.12), raising birds and occupational exposures to animal feeds, products and dusts and pesticides. Risk of IPF decreased significantly in male workers and insignificantly among female workers in sales and clerical related activities. The environmental exposures to birds and cats were significantly associated with elevated risk of IPF development in both sexes.

Conclusion: In Egypt, farming, raising birds and wood working are important risk factors for the development of IPF.

Keywords: Case-control studies; Egypt; Environment; Idiopathic pulmonary fibrosis; Occupations

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic fibroproliferative disorder, which consists of the progressive fibrosis of the interstitial spaces of the lung with subsequent loss of the normal parenchymal architecture that leads to respiratory failure and death.[1] In various populations, the estimated prevalence ratios for IPF, mostly based on case series and case reports, ranged from 6 to 32 per 100 000.[2] However, more recent studies have provided prevalence ratios of 20 per 100 000 adult males and 13 per 100 000 adult females which translates to incidence rates of 10.7 and 7.4 per 100 000 people per year for males and females, respectively.[3]

IPF is clinically characterized by persistent dyspnea, reduced lung volumes, impaired gas exchange, and a histological pattern of usual interstitial pneumonia (UIP) on surgical lung biopsy.[4,5]

The etiology of IPF is still unknown; it is considered a complex disorder with a strong interaction between a genetic background and environmental factors. However, so far suspected genes and environmental factors that consistently increase the risk of IPF have not been identified.[6] Some studies reported several potential etiologic factors of IPF including chronic exposure to domestic wood burning,[7] atopy,[8] Epstein-Barr virus,[9,10] hepatitis C virus,[11,12] adenovirus,[13] and genetic factors.[14] Some case-control studies have focused on potential risk factors including cigarette smoking,[15-18] atopy,[16,18] and occupational and environmental exposures related to activities associated with a high probability of dust or vapor inhalation including wood dusts, metal dusts and dusts related to farming activities and raising birds.[15,16,18]

Because epidemiologic information about the risk factors associated with the development of IPF in Egypt is limited, we conducted this multicenter hospital-based case-control study to identify occupational and environmental risk factors associated with the development of IPF in Egypt.

Patients and Methods

A multicenter hospital-based case-control study was carried out in chest hospitals and departments affiliated to three Egyptian cities—Cairo, Tanta and Mansoura—between January 2010 and January 2011.

All patients with confirmed IPF admitted during the study period to one of the collaborated hospitals in the previously mentioned cities and who agreed to participate in the research were included in this study. The diagnosis of IPF by the collaborating respiratory disease specialists was made based on the diagnostic criteria of American Thoracic Society and the European Respiratory Society[5] by history taking, clinical examination, high-resolution computerized tomography (HRCT) of the chest and pulmonary function testing (PFT). None of the cases accepted to confirm the diagnosis by either thoracoscopic lung biopsy or transbronchial lung biopsy. The presence of typical clinical and HRCT features of IPF, when identified by expert clinicians and radiologists, is sufficiently characteristic to allow a confident diagnosis and eliminate the need for surgical lung biopsy.[5] All cases had basal fine crackles in auscultation and predominantly peripheral, subpleural, bibasal fine reticular shadows and/or honeycombing, occasionally with traction bronchiectasis on HRCT. All cases had also abnormal pulmonary function studies including evidence of restriction—reduced vital capacity with increased FEV_1/FVC ratio. There was no evidence of either coexisting collagen-vascular disease or history of known occupational expo-

sure to agents that might produce a clinical picture similar to that of IPF in any of the cases. All eligible patients were asked to participate in this study; while 201 patients accepted to participate and were cooperative in answering the questions, 19 patients refused.

One control was selected to match each case for age (±3 years), sex, residence and smoking habits. These controls were selected from those patients admitted to the same wards of cases during the same period and who were treated for respiratory diseases other than interstitial pulmonary fibrosis. They were diagnosed as having chest infection (25%), bronchial asthma (28%), chronic obstructive pulmonary disease (26%), bronchiectasis (13%), pulmonary embolism (5%), and bronchogenic carcinoma (3%). Out of the 220 controls selected, only 205 accepted to participate in this study.

The study was approved by the Research Ethics Committee of Mansoura Faculty of Medicine. Written informed consent was taken from all studied participants.

All data were collected by interviewing through two questionnaires. One of the questionnaires elicited information from both cases and controls about personal information including age, sex, marital status, residence, educational level, smoking habits, type of job and exposure to 11 specific occupational agents and environmental exposures as moulds in the house and indoor domestic pets. Occupational data focused on type of job held for the longest period of time during the subject's work life and years of exposure. Occupational agents were considered "present" if the subject reported >10 h of exposure per week. The other questionnaire was to collect the clinical criteria of IPF, results of chest radiography (plain and HRCT), PFT, bronchoalveolar lavage and biopsy, whenever done, and investigations done to exclude collagen-vascular diseases.

TAKE-HOME MESSAGE

- Genetic background and environmental factors such as chronic exposure to domestic wood burning, atopy, Epstein-Barr virus, hepatitis C virus, adenovirus, may be the most etiologic factor of IPF.
- Wood and metal dusts, and dusts related to farming activities and raising birds are the most environmental and work-related exposure risk factors for IPF.
- The risk of IPF increased among male workers in carpentry or woodworking and chemical and petrochemical industry. Farming and raising birds were significant risk factors for the development of IPF among female workers.
- The environmental exposure to domestic birds and cats was positively associated with IPF development in both genders.

Statistical Analysis

Data were analyzed using SPSS® ver 11 for Windows® (SPSS Inc., Chicago, IL, USA). Both study groups were compared using the χ^2 test for qualitative variables and *Student's t* test for quantitative variables. Multiple logistic regression analysis was used to estimate the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) of IPF for single factors with adjustment for age, residence and smoking for both males and females. The reference category for job title, occupational and environmental factors was based on the comparison of those exposed to a single agent with all those unexposed, including potential subjects who were exposed to

Table 1: Sociodemographic criteria of studied groups

Parameter	Cases (n=201)	Controls (n=205)	p value
Mean±SD age	51.0±10.5	50.3±10.4	0.45
<30	7 (3.5%)	6 (2.9%)	0.84
30–44	54 (26.9%)	62 (30.2%)	
45–59	104 (51.7%)	105 (51.2%)	
≥60	36 (17.9%)	32 (15.6%)	
Sex			
Male	95 (47.3%)	114 (55.6%)	0.11
Female	106 (52.7%)	91 (44.4%)	
Marital status			
Married	186 (92.5%)	178 (86.8%)	0.07
Single	15 (7.5%)	27 (13.2%)	
Residence			
Urban	77 (38.3%)	64 (31.2%)	0.31
Suburban	41 (20.4%)	49 (23.9%)	
Rural	83 (41.3%)	92 (44.9%)	
Smoking			
Current smoker	52 (25.9%)	64 (31.20%)	0.17
Former smoker	8 (4.0%)	3 (1.5%)	
Never smoker	141 (70.1%)	138 (67.3%)	
Types of smoking			
Cigarette	52 (89.70%)	51 (76.10%)	0.06
Goza/Shesha	6 (10.30%)	16 (23.90%)	
Mean±SD Packs/year	380.06±186.98	331.65±195.48	0.19
Mean±SD duration (yrs)	23.27±9.41	23.95±9.64	0.69
Educational level			
Low	102 (50.7%)	98 (47.8%)	0.15
Moderate	73 (36.3%)	90 (43.9%)	
High	26 (12.9%)	17 (8.3%)	

other etiologic factors.

Results

Table 1 summarizes the demographic data of the studied groups. Both groups were matched for sociodemographic variables. Patients with IPF had an age range of 22 to 78 years; more than half of the patients belonged to the 45–59 year age group. The disease was reported more frequently in female (52.7%), residents of rural areas (41.3%), never smokers (70.1%), and those with low educational level (50.7%).

Clinical and laboratory characteristics of patients with IPF are demonstrated in Table 2. The mean±SD disease duration was 30.5±26.3 months. At the time of admission in the chest department, most of patients had grade IV dyspnea (53.2%), and grade I clubbing (69.2%); all of them had central cyanosis and bibasilar dry

Table 2: Clinical and laboratory characteristics of patients with IPF

Characteristics	Cases (n=201)
Mean±SD duration (month)	30.5±26.3
Grade of dyspnea	
I	3 (1.5%)
II	45 (22.4%)
III	46 (22.9%)
IV	107 (53.2%)
Grade of clubbing	
I	127 (63.2%)
II	62 (30.9%)
III	12 (6.0%)
Central cyanosis	201 (100%)
Bibasilar dry crackles	201 (100%)
Ground glass appearance on chest x-ray	201 (100%)
PFTs (% of predicted)	
FVC	62.4±13.0
FEV_1	66.2±14.0
FEV_1/FVC	102.7±11.2
Arterial blood gas	
pH	7.35±0.05
$PaCO_2$ (mm Hg)	40.7±12.1
Bicarbonate (mmol/L)	24.1±9.0
PaO_2 (mm Hg)	72.8±10.5
O_2sat (%)	85.2±13.4

crackles. Ground glass appearance on chest CT was also observed in all patients. Reduction in the percentage of predicted FVC was found in all patients. Normal or high FEV_1/FVC ratio was observed in all patients (Table 2). Additionally, the mean arterial PO_2 and O_2 saturation was lower than normal.

Table 3 presents the adjusted risks associated with studied factors for development of IPF. Among male workers, the risk of IPF increased significantly in chemical and petrochemical industries (OR=6.47, 95% CI: 1.66–25.1) as well as carpentry and wood working (OR=2.56, 95% CI: 1.02–7.01); the risk decreased significantly in activities related to sales (OR=0.11, 95% CI: 0.02–0.54) and clericals (OR=0.21, 95% CI: 0.02–0.52). Among female workers, the risk increased significantly in farming (OR=3.34, 95% CI: 1.17–10.12) as well as raising birds (OR=1.82, 95% CI: 1.03–3.85).

The risk of occupational exposures associated with the development of IPF after controlling for age, residence and smoking are shown in Table 4. For male workers, occupational exposures to wood dust and wood preservatives significantly increased the risk of development of IPF

Table 3: Associations of various occupations with development of IPF in studied men and women

Occupational groups	Men			Women		
	Control (%) (n=114)	Cases (%) (n=95)	OR* (95% CI†)	Control (n=91)	Cases (n=106)	OR (95% CI)
Clerical	11 (0.9)	3 (3)	0.21 (0.02–0.52)	9 (10)	0 (0.0)	—
Sales	17 (14.9)	2 (2)	0.11 (0.02–0.54)	7 (8)	3 (2.8)	0.35 (0.07–2.78)
Farming	28 (24.6)	20 (21)	1.00 (0.44–2.28)	7 (8)	22 (20.8)	3.34 (1.17–10.12)
Fishing	4 (3.5)	3 (3)	1.11 (0.22–5.60)	5 (5)	3 (2.8)	0.52 (0.11–2.33)
Hairdressing	1 (0.9)	2 (2)	1.89 (0.15–22.87)	10 (11)	11 (10.4)	1.01 (0.37–2.70)
Construction and Building demolition	14 (12.3)	11 (12)	0.96 (0.39–2.37)	—	—	—
Mechanics	12 (10.5)	10 (11)	0.96 (0.37–2.47)	—	—	—
Carpentry or woodworking	7 (6.1)	14 (15)	2.56 (1.02–7.01)	2 (2)	8 (7.5)	3.48 (0.67–18.16)
Chemical/ petrochemical	3 (2.6)	12 (13)	6.47 (1.66–25.12)	1 (1)	2 (1.9)	2.06 (0.17–23.89)
Painting	12 (10.5)	6 (6)	0.57 (0.20–1.62)	—	—	—
Raising birds	1 (0.9)	3 (3)	3.37 (0.31–36.16)	18 (20)	35 (33.0)	1.82 (1.03–3.85)
Textile making	2 (1.8)	5 (5)	2.76 (0.45–15.57)	7 (8)	4 (3.8)	0.63 (0.17–2.35)
Housewife	—	—	—	23 (25)	28 (29.4)	0.77 (0.38–-1.57)
Others	2 (1.80)	6 (6)	2.39 (0.40–14.30)	4 (4)	3 (2.7)	0.23 (0.02–2.13)

*OR: Odds ratio adjusted for age, residence and smoking (ever/never), †CI: Confidence interval

(OR=2.71, 95% CI: 1.01–7.37). In female workers, on the other hand, the risk of IPF development significantly increased with occupational exposures to animal feeds, products and dust (OR=1.78, 95% CI: 1.01–3.13) as well as pesticides (OR=8.68, 95% CI: 1.04–72.17).

The environmental exposures to birds and cats were significantly associated with elevated risk of IPF development in both men and women after controlling for age, residence and smoking (Table 5). The presence of home place moulds was not associated with development of IPF.

Discussion

The present study demonstrated the as-

Table 4: Associations of occupational exposures with development of IPF in studied men and women

Occupational exposures	Men			Women		
	Control (n=114)	Cases (n=95)	OR* (95% CI†)	Control (n=91)	Cases (n=106)	OR (95% CI)
Animal feeds, products and dust	27 (23.7)	16 (17)	0.65 (0.32–1.30)	42 (46)	64 (60.4)	1.78 (1.01–3.13)
Foods (vegetables, fruits, meat, fishes, seafood...)	4 (3.5)	2 (2)	0.48 (0.08–2.82)	2 (2)	1 (0.9)	1.01 (0.06–16.96)
Wood dust , wood preservatives	7 (6.1)	15 (16)	2.71 (1.01–7.37)	2 (2)	8 (7.5)	4.32 (0.84–22.12)
Insecticides/pesticide	6 (5.3)	8 (8)	2.24 (0.72–7.28)	1 (1)	9 (8.5)	8.68 (1.04–72.17)
Stone, clay, glass, concrete…	14 (12.3)	12 (13)	1.11 (0.45–2.72)	0 (0)	2 (1.9)	—
Metal dust/welding fumes	15 (13.2)	17 (18)	1.58 (0.69–3.61)	—	—	—
Solvents	12 (10.5)	12 (13)	1.06 (0.44–2.59)	0 (0)	1 (0.9)	—
Hair dyes	1 (0.9)	2 (2)	1.89 (0.15–22.87)	11 (12)	11 (10.4)	0.89 (0.34–2.31)
Textile dust	2 (1.8)	6 (6)	3.25 (0.60–17.56)	10 (11)	4 (3.8)	0.40 (0.11–1.38)
Others	2 (1.8)	6 (6)	3.15 (0.56–17.61)	3 (3)	2 (1.9)	0.64 (0.10–4.06)

*OR: Odds ratio adjusted for age, residence and smoking (ever/never), †CI: Confidence interval

sociations of some occupational and environmental factors in the development of IPF. The risk of IPF was found to be increased among male workers in carpentry or woodworking and chemical and petrochemical industry. Several studies found chemical fumes and dusts as important risk factors for IPF.[15-18,20] Although the mechanism is not well understood, it may be through their fibrogenic activity related to activation of oxygen species.[21] Furthermore, genetic susceptibility[22,23] and overwhelming of lung clearance mechanisms[24] are important contributing factors. Increased chance of fibrosis and extrinsic allergic alveolitis may be attributed to the exposure to wood dust, chemicals for wood protection, wood adhesives, and mold in wood.[16-18,25-27]

In the present study, farming and raising birds with the potential exposures to dusts of animal feeds, products and waste as well as pesticides were significant risk factors for the development of IPF among female workers. Also, the environmental exposure to domestic birds and cats was positively associated with IPF development in both genders. These findings

Table 5: Associations of environmental exposure with development of IPF in studied men and women

Environmental exposures	Men			Women		
	Control (n=114)	Cases (n=95)	OR* (95% CI†)	Control (n=91)	Cases (n=106)	OR (95% CI)
Birds	12 (10.5)	22 (23)	3.49 (1.49–8.19)	25 (27)	59 (56)	3.86 (1.95–7.62)
Cats	3 (2.6)	10 (11)	6.38 (1.59–25.56)	2 (2)	15 (14)	8.24 (1.80–37.70)
Dogs	6 (5.3)	8 (8)	1.94 (0.61–6.12)	2 (2)	8 (7.5)	3.63 (0.75–17.56)
Mold‡	19 (16.6)	15 (16)	0.68 (0.30–1.45)	23 (25)	25 (23.6)	1.37 (0.71–2.36)

*OR: Odds ratio adjusted for age, residence and smoking (ever/never), †CI: Confidence interval, ‡Any home place mold

were in accordance with Baumgartner, *et al*,[17] Iwai[15] and Gustafsson, *et al*.[27]

Agricultural workers are exposed to very high levels of dust and aerosolized particulates from a variety of sources including feed grains, bedding, and livestock fecal material,[28] and tend to have a higher prevalence of lung fibrosis.[29]

In Egypt, the poultry industry had expanded rapidly over the past 25 years to provide approximately 55% of the per capita animal protein consumption. Problems with raising birds in Egypt include widespread roof-top and back-yard raising bird, unhygienic local marketing and home slaughtering as well as the presence of approximately 40 000 poultry farms lacking biosecure and hygienic production systems and unprotected exposure to birds.[30,31] These widespread unplanned and unprotected activities in raising birds and their environmental impacts help in magnifying the role of raising birds in IPF development. In Egypt, women were found to be more involved in raising birds than men and this may explain the elevated risk of IPF among women.[32]

The risk of IPF development decreased significantly in males and insignificantly among females working as sellers and clericals. These findings were in agreement with Miyake and colleagues;[26] these may support the hypothesis of positive associations of IPF with dust-exposed occupations.[33]

There are several limitations to our study. First, the case-control study design. Second, the study conducted in three Egyptian cities only. Third, the IPF in patients was not confirmed by lung tissue biopsy. In addition, the study did not investigate the biological mechanisms of IPF development.

Despite of these limitations, the consistency of the observed positive associations of IPF development and working in occupations with dust exposure as wood working, chemical industries farming and raising birds, and the potential occupational exposure to dusts of wood, pesticides and animals, and the environmental exposures to dusts of birds and cats, may strengthen these associations and minimize the possibility of bias related

to the case-control study design. Furthermore, the study was multicenter carried out in three Egyptian cities with different population's demographic, occupational and environmental criteria; therefore, it may be considered as a valid approach for studying occupational and environmental risk factors in Egypt.

In conclusion, the present study confirms the results from previous epidemiologic studies about the positive association of IPF development and occupational and environmental dust exposures. In Egypt, farming, raising birds and wood working are important risk factors in IPF development after adjustment for age, smoking and residence.

Conflicts of Interest: None declared.

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