PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Effects of smoking, gender and occupational exposures on the risk of severe pulmonary fibrosis: a population based case-control study
AUTHORS	Ekström, Magnus; Gustafson, Torbjörn; Boman, Kurt; Nilsson, Kenneth; Tornling, Göran; Murgia, Nicola; Toren, Kjell

VERSION 1 - REVIEW

REVIEWER	Richard Kradin, M.D. Massachusetts General Hospital Boston, MA USA
REVIEW RETURNED	16-Oct-2013

GENERAL COMMENTS	The major concern is whether all of the population studied indeed has IPF. However, within the limits of the study design the findings are both noteworthy and interesting. Can the authors be a more specific concerning how the diagnosis of IPF was established, i.e., what percentage of diagnoses were made radiographically, clinically, versus pathologically? If that information is available, it would, in my opinion, be important to present it.

REVIEWER	R. Polosa University of Catania ITALY
REVIEW RETURNED	06-Nov-2013

GENERAL COMMENTS	In this in small retrospective case-control study, Ekstrom et al. have estimated the strengths of the association between smoking, gender, occupational exposures and the risk of developing severe pulmonary fibrosis. Their findings show that smoking has a dose-related association with increased risk of severe pulmonary fibrosis and that Swedish men with a combined history of smoking and occupational exposure are at particular high risk for developing severe pulmonary fibrosis. Below are my comments and recommendations: Major Points The notion that men with a history of smoking are a risk group for developing pulmonary fibrosis is well known. However, very little is known about the dose-response effect of cigarette smoking and even less is acknowledged about potential interaction effects with

	occupational exposure, an established risk factor for pulmonary fibrosis. Not many case-control studies have investigated these research themes and the data presented by Ekstrom et al. are welcomed. However, as for many case-control studies of this type, there is always a risk that the diagnosis is inaccurate; this is particularly compelling when considering that cases with a “probable” diagnosis of PF were collected between 1 February 1997 and 4 April 2000, prior to the dissemination and implementation of the first set of international guidelines on pulmonary fibrosis published in 2001. Collection of tobacco and occupational exposure data by the use of postal questionnaires is also likely to introduce bias. Details about type and timing of occupational exposure are not provided and are important. Interaction of cigarette smoking with occupational exposure may be dependent on the specific type of exposure; for example, smoking appears to be not influential in the development of PF in case of occupational exposure to metal dusts. It is mentioned in the text that the questionnaire has been described in detail elsewhere (ref.15), but I feel these details should be made available here as well. In addition, when appropriate, more exploratory ad hoc analyses should be conducted (for example, exploring wood dust exposure or exposure to bird individually). Last but not least, pulmonary fibrosis cases were selected from a Swedish national register (i.e. Swedevox) that includes patients starting LTOT for conditions associated with hypoxic respiratory failure (including pulmonary fibrosis) and using such a registry would increase the likelihood to include case with a mixed phenotypes, including cases with combined pulmonary fibrosis emphysema (CPFE), which is known to highly associated to smoking and male gender. This is likely to introduce a selection bias as the over-representation CPFE phenotypes in the Swedevox registry is likely to abnormally inflate OR for smoking in the "PF" cases (as in the case of the present study). CPFE is a newly coined diagnostic term and there is no way to disentangle true "PF" cases from the "Swedevox" registry retrospectively. However, this important limitation needs to be addressed in the Discussion. Currently, adult smoking prevalence in Sweden is just 13% far lower than the EU average of 28% and probably there are specific occupational exposure types and patterns. Therefore, the results obtained from a Swedish national register is unique to that population and cannot be generalized thus limiting the importance of these authors’ data. This need to be addressed in the Discussion. Please provide full details about smoking and occupational exposure in the control population.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1
Q1.1. Can the authors be more specific concerning how the diagnosis of IPF was established? What percentage of diagnoses were made radiographically, clinically, versus pathologically?

A1.1. We absolutely agree that this is an essential point, which has now been included in the revised manuscript. IPF was defined by excluding PF patients with an identifiable or probable secondary pulmonary fibrosis: the presence of rheumatic or systemic inflammatory diseases (20% of PF cases), pneumoconiosis (6%), medications or irradiation (2%). This has been added to the methods section. In addition, we have added the text below to the methods section:
"High-resolution computed tomography (HRCT) was performed in 41% of PF patients, CT in an additional 10%, and trans-bronchial and open lung biopsy was performed in 6%, respectively."

Reviewer #2
Q2.1. The IPF diagnosis might be inaccurate.

A2.1. We included only patients who started long-term oxygen therapy due to physician diagnosed pulmonary fibrosis. In addition, our IPF cohort was defined by 1) review of available medical records by respiratory physicians, and 2) by excluding patients with known or probable secondary pulmonary fibrosis. We have now included more details regarding this selection process in the methods selection, please see A1.1. We also discuss this limitation in the revised discussion section.

Q2.2. Details about type and timing of occupational exposures are not provided and are important. Interaction of cigarette smoking with occupational exposure may be dependent on the specific type of exposure.

A2.2. This is a very interesting issue. We have added the number and percentage of patients exposed to five categories of occupational exposure for PF patients, IPF patients and controls, respectively, in Table 1: any occupational exposure, exposure to birds, inorganic dust, metallic dust, organic dust and wood dust. Occupational data included the presence, start year, stop year and intensity (hours per week) for each exposure category. This and that a ten year lag-time was used as for smoking is now explicitly stated in the revised methods section.
We have added a new paragraph in the results section with effect estimates for subtypes of occupational exposure. Exposure to birds and wood dust were associated with increased adjusted risk of developing PF and IPF. There seemed to be similar interaction effects as in the main analysis (with any occupational exposure). There were no significant effects of inorganic dust or metal dust. This has been added to the paper in accordance with the reviewer's suggestion.

Q2.3. […] over-representation of combined pulmonary fibrosis and emphysema (CPFE) phenotypes is likely to abnormally inflate ORs for smoking in the PF cases.

A2.3. We agree that CPFE is likely to be present in our PF and IPF cohorts and that our data do not enable us to separate CPFE from non-CPFE. We now discuss this in the limitations paragraph in the revised discussion section. It is currently discussed whether CPFE is a smoking-related comorbidity or a distinct syndrome/phenotype of IPF. We now state in the discussion that CPFE could explain part of the association between smoking, male gender and the development with severe hypoxic PF in our study.

Q2.4. The results obtained from a Swedish national register is unique to that population and cannot

be generalized. […] This needs to be addressed in the discussion.

A2.4. We acknowledge that the external validity of the findings may be less in other settings. The following statement is now included in the revised discussion section: “Using national population based cases and controls, the present findings likely have high applicability to severe PF in Swedish clinical practice. The validity to other settings may be lower owing to differences in factors including socio-demographics, health care organization and patterns of exposure.”

Q2.5. Please provide full details about smoking and occupational exposure in the control population.

A2.5. Number and percentage of subjects within categories of smoking (smoking status and pack-years) and occupational exposure (birds, inorganic dust, metal dust, organic dust, and wood dust) are now provided in the revised Table 1. Details concerning the measurements and categories of occupational exposure have been added to the first paragraph in the methods section.

VERSION 2 – REVIEW

REVIEWER	Riccardo Polosa University of Catania - ITALY
REVIEW RETURNED	28-Nov-2013

- The reviewer completed the checklist but made no further comments.