

hilar lymphadenopathy and pulmonary lesions (figure 1). Pancreas biopsies revealed chronic pancreatitis. Accessory salivary gland and coeliac adenopathy biopsies showed non-caseating giant-cell epithelioid granuloma. The tuberculin purified protein derivative test and the Quantiferon assay were both negative. Laboratory analysis revealed a polyclonal hypergammaglobulinemia with IgG level at 35 g/l; serum IgG4 level was increased at 6.8 g/l (normal <0.8 g/l), white blood cell count revealed a lymphopenia (1000 mm³/l) and ACE was within the normal range.

Because of the histological picture of non-tuberculous granulomas, and mediastinal lymph nodes with pulmonary involvement on chest CT, sarcoidosis associated with an IgG4+ MOLPS was diagnosed. Corticosteroids (1 mg/kg/day) led to a dramatic improvement in the general and digestive manifestations within a 1-year follow-up.

AIP is a form of chronic pancreatitis characterised by a high serum IgG4 concentration and abundant IgG4-bearing plasma cell infiltration in the pancreatic lesion. This entity has been reported to be associated with a variety of extrapancreatic lesions. It is generally accepted that this form of pancreatitis is a part of a multi-systemic clinical syndrome, and this disease was redefined as 'IgG4-positive multi-organ lymphoproliferative syndrome'.²

Recently, Tsushima *et al*³ compared the clinicopathological features of pulmonary lesions in 19 patients with AIP and 8 patients with sarcoidosis; 17 of the 19 patients with AIP showed bilateral hilar lymphadenopathy, while 8 showed pulmonary nodules. IgG4-positive plasma cells were identified in the pulmonary lesions of patients with AIP. Our patient presented an authentic chronic pancreatitis with a significant increase in serum IgG4 level. She fulfilled the revised diagnostic criteria for AIP.⁴ Because of the presence of pulmonary lesions and hilar lymphadenopathies, salivary gland and coeliac adenopathies were biopsied, and they both revealed non-caseating epithelioid cell granulomas. Although sarcoidosis is uncommon in the elderly, the presence of disseminated granulomatous lesions led us to suspect sarcoidosis. However, it is difficult to determine whether our 80-year-old patient has an IgG4-related disease with systemic granulomatous lesions or an association of AIP with true sarcoidosis.

To our knowledge, such an association of AIP with granulomatous lesions mimicking sarcoidosis has never been reported previously in the literature, and this enlarges the spectrum of IgG4-related disease.

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Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; not externally peer reviewed.

Accepted 9 February 2011
Published Online First 17 April 2011

Thorax 2011;**66**:920–921.
doi:10.1136/thx.2011.160341

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CORRESPONDENCE

Gender differences in COPD: are women more susceptible to smoking effects than men?

We read the paper by Sørheim *et al*¹ with interest since possible clinical bias with regard to sex and disease in terms of diagnosis and treatment is clearly an important issue. The main problem with comparing the effect of a disease such as chronic obstructive pulmonary disease (COPD) between the two sexes is how one expresses the lung function deficit so that the data for the two sexes can be correctly analysed together.

We believe the method used by Sørheim *et al* introduces a sex bias that may be incorrectly influencing their result. The authors used percentage predicted to express the degree of abnormality and, depending on the equations used, this may bias the result with regard to sex and age.² Using the equations used by Sørheim *et al*,³ the scatter about the predicted value is the same for both sexes although the absolute predicted values for men are higher. This means that a man and a woman with forced expiratory volume in 1 s (FEV₁) values at equivalent deviation from predicted in population terms—for example, 1.645 standard deviations below predicted (equivalent to the 5th centile)—will have quite different percentage predicted values. Thus, for men of 1.80 m and women of 1.65 m (average height of the authors' prediction equations³) at the age of

25 years, the FEV₁ values at the 5th centile are 86.3% and 83.7% of predicted, respectively, and at the age of 70 they are 81.7% and 76.7% of predicted, respectively. In the paper by Sørheim *et al* the mean height of their subjects is not given but, assuming the above values and using the mean ages of the groups in table 1 in the paper, the 5th centile FEV₁ values would be at 82.5% and 78.6% predicted for the men and women, respectively, with COPD and 84.2% and 80.9% predicted for those without COPD.

This demonstrates how percentage predicted falsely suggests that subjects with equivalently low FEV₁ values in population terms appear to be different, with a bias towards women having apparently worse values than men. This bias is greater in older subjects and those with worse lung function. When using the ECCS prediction equations, this effect is still present but is much less than that seen with the equations used by Sørheim *et al*. Thus, using percentage predicted with the authors' prediction equations automatically makes low results for women appear worse than equivalently low results for men. We do not believe the paper by Sørheim *et al* has proved that women are more susceptible to smoking effects and their conclusion could well be an artefact based on the incorrect method used for expressing lung function abnormality. We suggest that the authors should rework their data with statistically valid methodology with their equations, such as using standardised residuals⁴ or centile values, and perhaps verify this with the generic equations of Stanojevic *et al*⁵ in order to determine if women are truly more susceptible than men to the effects of smoking.

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Competing interests None.

Provenance and peer review Not commissioned; not externally peer reviewed.

Accepted 18 October 2010
Published Online First 15 November 2010

Thorax 2011;**66**:921–922.
doi:10.1136/thx.2010.152348

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Author's response

We thank Dr Miller and colleagues for their valuable comments¹ on our recent article. Our findings² suggested a gender difference in susceptibility to the lung damaging effects of cigarette smoking. Female gender was associated with lung function reduction and more severe disease in COPD subjects with early-onset of disease or low smoking exposure. Interaction analysis also suggested that the effect of smoking on lung function might be different by gender.

Miller and colleagues question the use of lung function measurements expressed as per cent of predicted values, suggesting that this approach may introduce a gender bias. They argue that our prediction equations automatically make low results for women appear worse than equivalently low results for men.

FEV₁ expressed as per cent of predicted values was used as the outcome in several analyses in our article. As we pointed out in the discussion section of the article, we are fully aware that per cent of predicted values represent a potential limitation of the study. In the analyses of our article, we calculated predicted FEV₁ using Gulsvik reference equations.³ As mentioned in the article, we repeated our analyses using prediction equations from Johannessen *et al*⁴ and found that the main results were the same when changing the reference equations. To further verify our findings, we have now analysed our data using the equations of Stanojevic *et al*,⁵ as suggested by Miller and colleagues. All of our main findings were still valid.

In addition, we have estimated lower limit of normal (LLN, 5th centile) as 1.645 SDs below predicted to check for inherent gender bias in our study population across age groups. The point made by Miller and colleagues is important and their example showed that LLN in per cent predicted was lower for women than for men. To examine this issue further, we used four different reference equations (Gulsvik 2001,³ Johannessen 2006,⁴ Stanojevic 2008,⁵ Quanjer 1993⁶) and calculated LLN in per cent of predicted FEV₁ across age groups (40–50, 50–60, 60–70, >70) for men and women separately. As Miller points out, LLN in per cent of predicted FEV₁ declines with age. However, with the exception of men older than 70 years using Johannessen reference values and women older than 70 years using Quanjer values, LLN exceeded 80% predicted

for both genders across all age groups. Furthermore, an inherent gender bias is unlikely to explain the results in a population with our age and height distribution. If anything, the gender bias seemed to be towards men, in that men had slightly lower per cent predicted LLN than women—except when we used the Quanjer equations, where women had the lowest per cent predicted LLN.

In conclusion, both the rerun of our main analyses with alternative reference values and the additional estimations of LLN by gender suggest that our results are unlikely to be dependent on the use of FEV₁ in per cent predicted. We agree with Miller and colleagues that LLN in per cent of predicted FEV₁ clearly declines with age, and that there may be a gender bias depending on the reference equations used. To avoid results that are dependent on a specific set of reference values, alternative reference values should be applied to test the robustness of the initial results.

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Competing interests None.

Provenance and peer review Not commissioned; not externally peer reviewed.

Accepted 18 October 2010

Published Online First 20 November 2010

Thorax 2011;**66**:922. doi:10.1136/thx.2010.153478

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Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;**16**:5–40.

Utility of cytopathology in diagnosis and molecular testing of lung cancer

We read with interest the editorial by Booton *et al*¹ on advances in the treatment and diagnosis of non-small cell lung cancer. Recently published best practice guidelines for pathology recommend the provision of as precise a diagnosis as possible, with optimisation of specimen use.² We advocate the utility of cytopathology in this regard and share our experience of the diagnostic potential and the range of ancillary tests possible on respiratory-related cytology specimens.

During a 20-month period (1 September 2009 to 30 April 2011), 227 patients were diagnosed with lung cancer at our centre, 162 of whom (264 samples) had malignant cytology from a range of exfoliative (bronchial brushings, washings and lavages; pleural fluid) and fine needle aspiration samples, the latter encompassing transbronchial and transoesophageal ultrasound guided fine needle aspiration of mediastinal lymph nodes and lung. Patients had one to four samples each. Morphological diagnosis of keratinising squamous cell carcinoma could be made with confidence without the need for immunocytochemistry, and in experienced hands, cytological appearances of small cell carcinoma are also characteristic. Subtyping of other carcinomas was undertaken by means of immunocytochemistry performed on agar cell blocks, material permitting (table 1).

A morphological diagnosis of non-small cell carcinoma not otherwise specified, due to insufficient material for immunotyping, may still be clinically useful depending on other clinical and staging information. If required, extra material can be requested for further subtyping.

Epidermal growth factor receptor mutation testing was requested in 36 cases, with mutations identified in six patients. Three tests failed due to insufficient DNA. In some cases where testing was not possible due to insufficient sample, direct communication with the treating clinician was undertaken to request more material, for example, pleural fluid. Testing for ALK-EML4 fusion was performed in one case.

The strategic use and triage of cytological material enable the maximum diagnostic and therapeutic information to be obtained. This may entail using all of the material in a sample for ancillary tests without producing traditional diagnostic slides, when the diagnosis has already been established in preceding samples. Close collaboration with