LETTERS

Subsequent COPD and lung cancer in patients with autoimmune disease

To the Editors:

Autoimmune diseases can be defined as clinical syndromes caused by the activation of T-cells or B-cells, or both, in the absence of an ongoing infection or other discernible cause [1]. These cells recognise specific foreign antigens but even in healthy individuals they possess a low-level of autoreactivity towards own antigens. Autoreactivity is increased in auto-immune diseases either systemically (as in rheumatoid arthritis) or organ-specifically (Graves' disease and type 1 diabetes mellitus). These diseases are diagnosed by clinical symptoms and by specific types of autoantibodies. The prevalence of autoimmune diseases ranges from 5–10% of the population in Western countries, including common diseases, such as rheumatoid arthritis and autoimmune thyroiditis, and many rare ones [2]. Epidemiological studies have demonstrated that genetic factors are crucial determinants of susceptibility to autoimmune disease [1]. For many of these diseases a familial clustering is reported. However, even in a genetically predis-posed person, some trigger, an environmental exposure or a change in the internal environment, is usually required to precipitate autoreactivity [3]. Smoking is an environmental risk factor for some autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, Graves' disease and primary biliary cirrhosis, but for many other autoimmune diseases data on smoking are either lacking or controversial.

Chronic obstructive pulmonary disease (COPD) is a slowly progressive disease characterised by irreversible airflow limitation, which is caused by chronic inflammatory immune response to inhaled gases and particles [4]. It may affect up to 10% of the population. In the early phase, the inflammatory process is located in central airways but in progressive disease the distal airspaces are enlarged because of destruction of airway walls. In some cases only small airways are obstructed with minor impairment in lung function tests. Increasing lines of evidence show that autoimmune mechanisms are involved in COPD [4]. α-Antitrypsin deficiency is an established genetic risk factor of emphysema, but its prevalence is <0.1% in the population and thus it will account for a small proportion of COPD [5]. Tobacco smoking is the single most common risk factor for COPD but even many other environmental factors are known [5]. In smokers of >40 pack-yrs, the prevalence of COPD has been reported to be >50% [6]. Smoking is a shared risk factor for COPD and lung cancer.

In the present paper, we examine associations of autoimmune diseases, COPD and lung cancer, first to test for a possible shared aetiology between autoimmune disease and COPD, and secondly to test for a possibility that smoking may be a risk factor of autoimmune diseases.

The autoimmune disease and COPD research database, used for this study, was constructed by linking several national Swedish registers, as has been described earlier [7, 8]. Data on autoimmune diseases and COPD were obtained from the Swedish Hospital Discharge Register that records complete data on all discharges with dates of hospitalisation and diagnoses in some regions since 1964 and nationwide since 1986; cancer data were retrieved from the Swedish Cancer Registry. All linkages were performed by the use of an individual national identification number that is assigned to each person in Sweden for their lifetime. This number was replaced by a serial number for each person in order to provide anonymity.

The International Classification of Diseases codes used have been previously described [7, 9]. Risk of COPD and lung cancer was determined for persons who had been hospitalised for autoimmune disease any time between 1964 and 1999 compared with persons who had not been hospitalised for autoimmune disease. Person-yrs were calculated for COPD and lung cancer from start of follow-up on January 1, 2000 until hospitalisation for COPD or lung cancer, death, emigration or closing date on December 31, 2006. Patients hospitalised for COPD or diagnosed with lung cancer prior to the year 2000 were excluded. The reasons for starting the follow-up in the year 2000 were to allow for uniform diagnostics and to exclude the possible lead time bias that hospitalisation and the resulting medical examinations may cause [8, 9]. This decision implied that for some patients the time difference between hospitalisa-tions for autoimmune disease and COPD/lung cancer was long, which could lead to increased risks. Standardised incidence ratios (SIRs) were calculated as the ratio of observed to expected number of cases. The expected number of cases was calculated for age (5-yr groups), sex, period (5-yr groups), region and socioeconomic status-specific standard incidence rates.

In table 1, 29 autoimmune diseases are shown with at least five patients diagnosed in each with COPD; four other diseases are not shown because only one or no COPD was diagnosed. The risk of COPD was increased in patients hospitalised for 18 different autoimmune diseases (the total patient number was 297,300), among which the highest SIRs were observed for polyarteritis nodosa (5.69), primary biliary cirrhosis (4.79), pernicious anaemia (4.04), polymyalgia rheumatic (3.77), Addison disease (3.56), myasthenia gravis (3.27), chronic rheumatic heart disease (3.13) and systemic sclerosis (3.08) (all over 3.00). The SIR for all included autoimmune diseases was 1.99 in 1,474 COPD patients. The SIR for type 1 diabetes was decreased to 0.42.

According to table 1, high risks of lung cancer were observed in systemic sclerosis (4.45), discoid lupus erythematosus (4.24)

TABLE 1 Risk of chronic obstructive pulmonary disease (COPD) and lung cancer since the year 2000 in patients hospitalised for autoimmune disease before the year 2000

Autoimmune disease	COPD				Lung cancer			
	Person yrs	Obs.	SIR	95% CI	Person yrs	Obs.	SIR	95% CI
Addison's disease	5195	10	**3.56**	1.69–6.57	6353	3	0.87	0.16–2.57
Amyotrophic lateral sclerosis	2773	7	2.22	0.88–4.60	2907	0		
Ankylosing spondylitis	21279	41	**1.72**	1.23–2.33	24116	11	0.72	0.36–1.29
Behçet's disease	10627	9	0.94	0.43–1.80	10867	7	1.15	0.45–2.37
Celiac disease	25277	12	0.59	0.31–1.04	31288	3	1.26	0.24–3.74
Chronic rheumatic heart disease	20121	85	**3.13**	2.50–3.88	20976	20	0.93	0.57–1.44
Crohn's disease	117202	132	1.18	0.99–1.40	130065	60	1.05	0.80–1.35
Diabetes mellitus type 1	80525	24	**0.42**	0.27–0.62	89180	1	0.48	0.00–2.77
Discoid lupus erythematosus	1515	6	**2.98**	1.07–6.53	1927	6	**4.24**	1.53–9.29
Graves'/hyperthyroidism	107993	204	**2.37**	2.05–2.71	108500	80	1.23	0.98–1.53
Hashimoto/hypothyroidism	22488	58	**2.78**	2.11–3.60	24586	21	1.35	0.84–2.07
Immune thrombocytopenic purpura	8215	6	1.23	0.44–2.69	8664	4	2.10	0.55–5.44
Localised scleroderma	14138	21	1.36	0.84–2.08	14398	9	1.20	0.55–2.30
Multiple sclerosis	33398	45	1.03	0.75–1.39	35891	18	0.86	0.51–1.36
Myasthenia gravis	50058	111	**3.27**	2.69–3.94	49010	46	1.02	0.74–1.36
Pernicious anaemia	9954	25	**4.04**	2.61–5.97	9980	10	0.94	0.45–1.73
Polyarteritis nodosa	11688	45	**5.69**	4.15–7.62	11824	9	0.76	0.35–1.46
Polymyalgia rheumatica	41301	146	**3.77**	3.18–4.44	42628	36	0.90	0.63–1.25
Polymyositis/dermatomyositis	2821	6	1.93	0.69–4.23	3484	8	**3.92**	1.67–7.76
Primary biliary cirrhosis	2467	8	**4.79**	2.05–9.49	2861	2	0.89	0.08–3.27
Psoriasis	46377	101	**2.44**	1.99–2.97	50146	44	1.33	0.97–1.79
Rheumatic fever	13327	28	**2.05**	1.36–2.97	13786	10	1.09	0.52–2.02
Rheumatoid arthritis	64834	181	**2.57**	2.21–2.97	103101	118	**1.48**	1.23–1.77
Sarcoidosis	31471	57	**1.85**	1.40–2.40	32410	17	0.85	0.50–1.37
Sjögren's syndrome	8661	18	**1.89**	1.12–2.99	10075	5	0.79	0.25–1.85
Systemic lupus erythematosus	13363	33	**2.29**	1.57–3.21	16775	23	**2.72**	1.72–4.09
Systemic sclerosis	2555	6	**3.08**	1.11–6.74	3882	11	**4.45**	2.21–7.99
Ulcerative colitis	53018	44	1.27	0.92–1.70	77761	33	1.11	0.76–1.56
Wegener granulomatosis	2004	5	1.66	0.52–3.90	2228	2	1.10	0.10–4.04
All	826614	1474	**1.99**	1.89–2.09	941554	617	**1.18**	1.09–1.27

Obs.: observed; SIR: standardised incidence ratios. Numbers shown in bold font: 95% CIs do not overlap with 1.00.

and polymyositis/dermatomyositis patients (3.92). Also systemic lupus (2.72) and rheumatoid arthritis (1.48) were associated with lung cancer. Overall, 617 patients with an SIR of 1.18 were diagnosed with lung cancer.

The use of the Hospital Discharge Register to identify patients with autoimmune diseases offers access to a nationwide patient pool with a reasonably high diagnostic accuracy; the discharge diagnoses are often delivered by specialists during extended examinations in the clinic. However, the degree of hospitalisation for the covered autoimmune diseases probably vary extensively depending on the seriousness of the condition and alternative forms of treatment, as we have discussed for some of the covered diseases elsewhere [8, 9]. For some diseases most patients have been hospitalised in the course of the disease, including hyperthyroidism, Crohn's disease, ulcerative colitis, type 1 diabetes and rheumatoid arthritis. For these, the estimated risks for COPD appear generally valid. For other autoimmune diseases with a lower degree of

hospitalisation, such as hypothyroidism, the data may be valid only for the hospitalised portion of the patient population.

In the present study, 18 autoimmune diseases were associated with COPD and five with lung cancer. The diseases associated with COPD included rheumatoid arthritis, systemic lupus erythematosus, Graves' disease, primary biliary cirrhosis, polymyalgia rheumatica and psoriasis, for which smoking is a known risk factor [3, 10]. However, the remarkable lack of excess lung cancer in patients with the five highest risk autoimmune diseases (polyarteritis nodosa, pernicious anaemia, Addison's disease, myasthenia gravis and chronic rheumatic heart disease) is a strong indication of an autoimmune contribution to COPD. It was also interesting that the associations of polymyositis/dermatomyositis with lung cancer showed no significant (although increased) risks for COPD. The risks for lung cancer in patients with systemic sclerosis, discoid lupus erythematosus and polymyositis/ dermatomyositis were remarkably high, around 4 or more,

which may suggest shared predisposition to these autoimmune diseases and lung cancer. Advice on smoking control would be appropriate for patients with these diseases.

In conclusion, the increased risk of COPD but not lung cancer in patients with many autoimmune diseases suggests that the defined autoimmunity may predispose to COPD. Another possibility is that smoking is a risk factor for some of these autoimmune diseases and the effects on lung cancer cannot be recognised because of the small number of cases. This possibility could not be ruled out because data on smoking were lacking. The four-fold risks of lung cancer in patients with systemic sclerosis, discoid lupus erythematosus and polymyositis/dermatomyositis may indicate susceptibility to lung cancer, which should be considered in the counselling of these patients.

K. Hemminki*,#, X. Liu#, J. Ji#, K. Sundquist# and J. Sundquist#,¶

*Division of Molecular Genetic Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany, #Center for Health Care Research, Lund University, Malmö, Sweden, and ¶Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, CA, USA.

Correspondence: K. Hemminki, DKFZ, Im Neuenheimer Feld 580, D-69120 Heidelberg, Germany. E-mail: k.hemminki @dkfz.de

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Clinical features of secondary pulmonary alveolar proteinosis: pre-mortem cases in Japan

To the Editors:

Pulmonary alveolar proteinosis (PAP) is a rare syndrome that predominantly affects the lungs, and is characterised by the accumulation of surfactant lipids and proteins in the alveoli and terminal airways [1]. In 1999, we published findings that high levels of granulocyte-macrophage colony-stimulating factor (GM-CSF) neutralising autoantibodies were detected specifically in patients with idiopathic PAP [2]. Recently, as a result of the excellent sensitivity and specificity of GM-CSF autoantibody assays in identifying this form of PAP [3], it has been proposed that the nomenclature for this condition should be changed to ''autoimmune PAP'' rather than ''idiopathic PAP'' [4]. Secondary or hereditary PAP is not associated with

GM-CSF autoantibodies but develops as a consequence of a separate underlying disorder or genetic background [5]. Recently, we demonstrated that the characteristic high-resolution computed tomography (HRCT) findings in secondary PAP are distinct from those in autoimmune PAP [6]. However, physicians may not suspect secondary PAP, even when encountering unexplained pulmonary opacities on chest radiograph or computed tomography in patients with pre-existing haematological or infectious diseases, since there is little information available on the clinical features. Here, we outline the clinical features of adult-onset secondary PAP based on our database of 40 pre-mortem cases in which serum GM-CSF autoantibodies were negative, and compare them with other cases in the literature.