Effect of autoimmune diseases on risk and survival in histology-specific lung cancer

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ABSTRACT: Patients with autoimmune diseases are at an increased risk of cancer due to underlying dysregulation of the immune system or treatment. Data on cancer incidence, mortality and survival after autoimmune diseases would provide further information on the clinical implications.

We systematically analysed data on lung cancer in patients diagnosed with 33 different autoimmune diseases. Standardised incidence ratios (SIRs), standardised mortality ratios (SMRs) and hazard ratios (HRs) were calculated for subsequent incident lung cancers or lung cancer deaths up to 2008 in patients hospitalised for autoimmune disease after 1964.

Increased risks of lung cancer were recorded for SIRs after 12 autoimmune diseases, SMRs after 11 autoimmune diseases and HRs after two autoimmune diseases. The highest SIRs and SMRs, respectively, were seen after discoid lupus erythematosus (4.71 and 4.80), polymyositis/dermatomyositis (4.20 and 4.17), systemic lupus erythematosus (2.47 and 2.69), rheumatic fever (2.07 and 2.07) and systemic sclerosis (2.19 and 1.98). Autoimmune disease did not influence survival overall but some autoimmune diseases appeared to impair survival in small cell carcinoma.

All autoimmune diseases that had an SIR >2.0 are known to present with lung manifestations, suggesting that the autoimmune process contributes to lung cancer susceptibility. The data on survival are reassuring that autoimmune diseases do not influence prognosis in lung cancer.

KEYWORDS: Comorbidity, immune disturbance, prognosis, risk, treatment

Autoimmune diseases constitute many disease manifestations which jointly affect 5–10% of the population in developed countries [1]. Autoimmune diseases are characterised by the activation of T-cells or B-cells, or both, in the absence of an ongoing infection. The normal function of these cells is to recognise specific foreign antigens, but they also possess a low level of autoreactivity towards self- or auto-antigens. In autoimmune diseases, autoreactivity is increased either systemically or organ-specifically [2]. Many cancers, for reasons that are not known, are increased in autoimmune disease patients [3–6]. The immunological disturbances in autoimmune diseases may be an important mechanism in cancer formation, but immunosuppressive therapy may also contribute [7].

Lung and pleural manifestations of systemic autoimmune disease are heterogeneous [8]. They may not only affect lung parenchyma, but may involve the conducting airways, respiratory muscles and pulmonary vasculature. Common features of disease presentation are pleuritis with effusion and interstitial progressive lung disease. Pleural

effusions are also caused by infections, which need to be excluded. Rheumatoid nodules in the airways may mimic neoplastic growth and require differential diagnostics. Pleuropulmonary disease is a common feature of systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, polymyositis/dermatomyositis, Sjögren's syndrome, granulomatosis with polyangiitis (Wegener's) and sarcoidosis [8].

Lung cancer risks have been associated with systemic lupus erythematosus, rheumatoid arthritis, Crohn's disease, psoriasis and sarcoidosis [9–14]. No increase has been observed in ulcerative colitis patients [15]. Some studies have analysed survival in lung cancer after an autoimmune disease; decreased survival was noted after sarcoidosis, Crohn's disease and ulcerative colitis, but no effect was reported after psoriasis and rheumatoid arthritis [16–19].

In the present study we examined the risk of lung cancer (standardised incidence ratio (SIR)), mortality in lung cancer (standardised mortality ratio (SMR)) and survival in lung cancer (hazard ratio

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(HR)) in patients who had been hospitalised for any one of 33 autoimmune diseases, in the total Swedish population. Lung cancer manifests in various histological types and it is of interest to assess the various outcome measures by histology, for which hardly any data are available. Many autoimmune diseases show large sex differences and, therefore, a sex-specific analysis was also included.

MATERIAL AND METHODS

The research database used in the present study is a subset of the national MigMed 2 datasets from the Center for Primary Health Care Research, Lund University, Malmö, Sweden. It has been used in our previous studies on autoimmune disease and various cancers, whereby the methods used have been identical, except for the cancer under study [6, 20, 21]. Autoimmune disease patients were identified from the Swedish Hospital Discharge Register which records complete data on all discharges with dates of hospitalisation and diagnoses in some regions since 1964 and nationwide since 1986. The International Classification of Diseases codes have been described previously [22, 23]. A total of 33 diseases were covered. However, seven of them had less than 11 cases for lung cancer, therefore, data are not shown for autoimmune haemolytic anaemia, chorea minor, lupoid hepatitis, polyarteritis nodosa, polymyalgia rheumatic, Reiter's disease and type 1 diabetes; these diseases were not significantly associated with lung cancer. The linkages were performed using an individual national identification number that is assigned to each person in Sweden for life. This number was replaced by a serial number for each person in order to provide anonymity.

Cancer data were obtained from the nationwide Swedish Cancer Registry. Person-yr of follow-up were calculated from date of discharge with the first main diagnosis of autoimmune disease until death, emigration or closing date, December 31, 2008. SIRs were calculated as the ratio of observed to expected number of lung cancers. SMRs were similarly calculated as the ratio of observed to expected number of cancer-specific deaths. Expected numbers were calculated for anyone not hospitalised for any autoimmune disease. The expected numbers were calculated as age (5-yr groups), sex, period (5-yr groups), region and socio-economic status-specific standard incidence rates. Additional adjustments were made for hospitalisation for obesity using codes: ICD-7 287.00, 287.09; ICD-8 277.99; ICD-9 278A; and ICD-10 E65–E68. A total of 30,020 individuals had been hospitalised for obesity. Similar adjustments were made for hospitalisation for chronic obstructive pulmonary disease (COPD) (as a surrogate for smoking), with 260,243 individuals affected (codes: ICD-7 500–502; ICD-8 490–493; ICD-9 490–496; and ICD-10 J40–J49) and alcoholism (codes: ICD-9 303; and ICD-10 F10.1–F10.9), with 181,862 individuals affected. Confidence intervals were calculated assuming a Poisson distribution. The Cox regression analyses were used to estimate HRs, which could be interpreted as mortality rate ratio. Adjustments were performed as above. The analyses were for deaths in lung cancer while deaths from other causes were censored. The reference population was anyone not hospitalised for any autoimmune disease, as for SIR and SMR. The proportional hazard assumption for the covariates was tested by Schoenfeld residuals and by plotting the log of the negative log of the survival function *versus* the log of time. The study was approved by the regional ethical review board at Lund University.

RESULTS

The total number of autoimmune disease patients was 402,062 and they accumulated 4.8 million person-yr at risk (mean follow-up 11.9 yrs). Table 1 shows the numbers of patients for each autoimmune disease; the largest individual disease was rheumatoid arthritis with 72,309 patients. Of the 33 autoimmune diseases analysed, 26 had more than 10 cases of lung cancers and these are shown in table 1. For lung cancer after any autoimmune disease, including the ones not shown, SIR was 1.33, SMR was 1.26 and HR was 1.02 (not significant). SIRs (12 increases, one decrease) and SMRs (11 increases, one decrease) correlated and, even though neither was statistically significant, the direction (increase or decrease) was almost always the same (table 1). For this reason SMR are only shown in table 1. The highest SIRs and SMRs, respectively, were seen after discoid lupus erythematosus (4.71 and 4.80), polymyositis/dermatomyositis (4.20 and 4.17), systemic lupus erythematosus (2.47 and 2.69), rheumatic fever (2.07 and 2.07) and systemic sclerosis (2.19 and 1.98). SIR was decreased in pernicious anaemia patients (0.70). Only after amyotrophic lateral sclerosis was HR increased (1.60); patients with coeliac disease (0.49) and rheumatic fever (0.76) showed favourable survival.

None of the individual SIRs differed significantly (95% confidence interval overlapping) by sex (table 2), nor did the overall SIRs (1.29 for females and 1.36 for males). SIRs for lung cancer after Crohn's disease were only significant for females and those after chronic rheumatic heart disease, Hashimoto's disease/hypothyroidism and sarcoidosis were only significant for males. The only significant HR for females was for pernicious anaemia patients (2.12), for males it was 1.03, but the difference was not significant. Males with polymyositis/dermatomyositis (HR 1.72) and rheumatoid arthritis (HR 1.15) had decreased survival. Male coeliac disease patients showed a favourable survival (HR 0.50).

Table 3 presents results according to the four main histological types. The overall case numbers were approximately equal for adenocarcinoma (n=741) and for squamous cell carcinoma (n=740), which were double that of small cell carcinoma (n=388); large cell carcinoma had intermediate case numbers (n=615). The overall SIRs increased after autoimmune disease for all histological types, but mostly for small cell (1.43) and squamous cell (1.40) carcinoma. Squamous cell carcinoma was increased after nine autoimmune diseases, large cell carcinoma after eight autoimmune diseases, small cell carcinoma after seven autoimmune diseases and adenocarcinoma after five autoimmune diseases. All types of lung cancer were increased after discoid lupus erythematosus and the highest risk was for small cell carcinoma (7.36, the highest risk in the study). Similarly, all lung cancer histologies were increased after polymyositis/dermatomyositis, systemic lupus erythematosus, rheumatoid arthritis and psoriasis; however, for the latter two, the adenocarcinoma increase was of borderline significance. Again, none of the SIRs differed significantly (95% confidence intervals overlapping) between the histological types. Squamous cell carcinoma was only increased after primary biliary cirrhosis (5.10). Adenocarcinoma and squamous cell carcinoma were increased after rheumatic fever and systemic sclerosis. Large cell carcinoma and small cell carcinoma were increased after thyroid disease. The only significant decrease in SIR was 0.40 for adenocarcinoma after pernicious anaemia.

TABLE 1 Standardised incidence ratios (SIRs), standardised mortality ratios (SMRs) and hazard ratios (HRs) for lung cancer after a specified autoimmune disease

Autoimmune disease	Cases	Person-yr	Observed	SIR (95% CI)	Person-yr	Deaths	SMR (95% CI)	Person-yr	HR (95% CI)
Addison's disease	3010	33138	20	1.37 (0.84–2.12)	36546	17	1.35 (0.78–2.16)	20	1.49 (0.94–2.37)
Amyotrophic lateral sclerosis	7623	27844	21	1.24 (0.77–1.90)	29651	18	1.31 (0.77–2.07)	11	1.60 (1.02–2.51)
Ankylosing spondylitis	6646	112837	56	1.10 (0.83–1.43)	116968	41	1.05 (0.75–1.43)	47	1.15 (0.84–1.57)
Behcet's disease	3874	63199	31	1.26 (0.86–1.80)	66131	25	1.33 (0.86–1.96)	59	0.79 (0.52–1.18)
Coeliac disease	11459	216253	22	1.09 (0.68–1.65)	219248	14	0.86 (0.47–1.44)	60	0.49 (0.29–0.84)
Chronic rheumatic heart disease	21027	166284	165	1.25 (1.06–1.45)	180247	96	0.95 (0.77–1.16)	263	1.00 (0.85–1.19)
Crohn's disease	25677	392323	152	1.36 (1.15–1.60)	407708	121	1.32 (1.10–1.58)	229	1.03 (0.86–1.23)
Discoid lupus erythematosus	870	12896	31	4.71 (3.20–6.70)	13819	25	4.80 (3.10–7.10)	43	1.21 (0.84–1.75)
Graves' disease/hyperthyroidism	42020	541195	330	1.34 (1.20–1.49)	581105	259	1.27 (1.12–1.44)	488	0.98 (0.87–1.10)
Hashimoto's disease/hypothyroidism	13160	120749	75	1.19 (0.93–1.49)	131196	53	1.01 (0.76–1.32)	143	0.88 (0.68–1.15)
Immune thrombocytopaenic purpura	4324	44244	19	1.77 (1.07–2.77)	46174	12	1.16 (0.60–2.03)	24	0.64 (0.33–1.23)
Localised scleroderma	1080	11819	12	1.91 (0.98–3.34)	13252	11	2.05 (1.02–3.68)	7	1.71 (0.95–3.09)
Multiple sclerosis	14616	185034	71	0.95 (0.74–1.20)	192765	57	1.01 (0.76–1.31)	97	1.28 (0.99–1.67)
Myasthenia gravis	3044	32670	18	1.04 (0.61–1.65)	37031	21	1.33 (0.82–2.04)	39	0.81 (0.48–1.36)
Pernicious anaemia	11590	67122	45	0.70 (0.51–0.94)	73860	44	0.90 (0.66–1.21)	30	1.22 (0.88–1.69)
Polymyalgia rheumatic	27534	253122	202	1.05 (0.91–1.20)	278201	173	1.04 (0.89–1.20)	268	1.02 (0.87–1.19)
Polymyositis/dermatomyositis	2465	24058	52	4.20 (3.13–5.51)	26122	44	4.17 (3.03–5.60)	45	1.12 (0.82–1.52)
Primary biliary cirrhosis	1874	13028	13	1.46 (0.77–2.50)	14187	10	1.32 (0.63–2.45)	22	0.92 (0.49–1.70)
Psoriasis	19777	276007	224	1.58 (1.38–1.80)	292523	153	1.36 (1.15–1.59)	279	1.02 (0.88–1.19)
Rheumatic fever	4306	77407	76	2.07 (1.63–2.60)	81308	58	2.07 (1.57–2.68)	123	0.76 (0.59–0.98)
Rheumatoid arthritis	72309	732085	673	1.47 (1.36–1.58)	782948	509	1.38 (1.26–1.51)	796	1.06 (0.98–1.16)
Sarcoidosis	11571	177824	104	1.29 (1.06–1.57)	189423	90	1.39 (1.12–1.71)	152	1.20 (0.97–1.48)
Systemic lupus erythematosus	7624	86640	85	2.47 (1.97–3.05)	91669	73	2.69 (2.11–3.38)	86	1.23 (0.98–1.54)
Systemic sclerosis	7169	90023	88	2.19 (1.76–2.70)	94897	61	1.98 (1.51–2.54)	108	1.11 (0.88–1.40)
Ulcerative colitis	33493	486800	155	0.93 (0.79–1.08)	510244	111	0.81 (0.67–0.97)	299	0.85 (0.71–1.02)
Granulomatosis with polyangiitis	15833	115785	101	1.02 (0.83–1.24)	128143	80	1.07 (0.85–1.33)	85	1.10 (0.89–1.37)
All	402462	4778630	2871	1.33 (1.28–1.38)	5059749	2195	1.26 (1.21–1.31)	3863	1.02 (0.98–1.06)

Data are presented as n, unless otherwise specified. Bold indicates that the 95% CI does not include 1.00.

As shown in table 3, the overall HRs were close to unity for all histologies except for large cell carcinoma (1.13). Survival did not differ from the reference group for any autoimmune disease patients diagnosed with adenocarcinoma or squamous cell carcinoma. Rheumatic polymyalgia and psoriasis had a decreased survival in large cell carcinoma (HR 1.51 and 1.39, respectively). Small cell carcinoma showed impaired survival after five autoimmune diseases, worst after amyotrophic lateral sclerosis (HR 5.49) and discoid lupus erythematosus (HR 2.83).

DISCUSSION

The present study of 402,062 autoimmune disease patients showed an increased risk of lung cancer for patients with 12 different autoimmune diseases. The overall SIR was 1.33 and the risk was increased after the common autoimmune diseases, rheumatoid arthritis (1.47), Graves' disease/hyperthyroidism (1.34) and Crohn's disease (1.36). This is the largest published study and the only one comparing systematically risk (SIR), mortality (SMR) and survival (HR). As lung cancer is a fatal disease, SMRs correlated closely with SIRs. Autoimmune disease did not impair overall survival, for which the HR was 1.02. Diagnoses of autoimmune diseases, based on discharge data, are

of high quality as hospitalised patients are seen by many doctors, often in specialist departments. A recent review on the validity aspects of the Swedish Hospital Discharge Register reported diagnostic accuracy (positive predictive values) for various autoimmune diseases, ranging from 74% for inflammatory bowel disease to 96% for rheumatoid arthritis [24].

Coverage is another issue that depends, for example, on the severity of the condition. The aforementioned review cited 42.5% for rheumatoid arthritis as the only autoimmune disease [24]. We have discussed coverage in many of our previous papers on familial clustering of autoimmune diseases [25–28]. Severe debilitating conditions, such as Graves' disease, type 1 diabetes mellitus, Crohn's disease and ulcerative colitis lead to hospitalisation at one point or another in Sweden. In contrast, Hashimoto's disease/hypothyroidism is an example of a disease with a low degree of hospitalisation. The Swedish Cancer Registry records all new cases of cancer and close to 100% of the cases are histologically or cytologically confirmed.

An unavoidable issue in the study of lung cancer is smoking, and whether it is a confounder in the present study. If smoking caused an autoimmune disease then the present observations

TABLE 2 Standardised incidence ratios (SIRs) and hazard ratios (HRs) for lung cancer after a specified autoimmune disease by sex

Autoimmune disease	Female						Male					
	Person-ys	Cases	SIR (95% CI)	Deaths	Person-ys	HR (95% CI)	Person-ys	Observed	SIR (95% CI)	Deaths	Person-ys	HR (95% CI)
Addison's disease	18958	8	1.08 (0.46–2.13)	8	14	1.22 (0.58–2.56)	14180	12	1.67 (0.86–2.93)	9	6	1.76 (0.98–3.17)
Amyotrophic lateral sclerosis	11456	6	1.49 (0.54–3.27)	6	4	1.43 (0.54–3.81)	16388	15	1.17 (0.65–1.93)	12	8	1.65 (1.00–2.74)
Ankylosing spondylitis	32767	11	1.01 (0.50–1.82)	7	12	0.96 (0.43–2.14)	80070	45	1.13 (0.82–1.51)	34	35	1.19 (0.85–1.67)
Behcet's disease	19524	10	1.67 (0.80–3.09)	10	18	0.97 (0.48–1.93)	43675	21	1.13 (0.70–1.73)	15	41	0.71 (0.43–1.18)
Celiac disease	128558	10	1.01 (0.48–1.86)	7	19	0.47 (0.20–1.13)	87695	12	1.17 (0.60–2.05)	7	41	0.50 (0.25–0.99)
Chronic rheumatic heart disease	86111	44	1.01 (0.73–1.36)	26	72	1.01 (0.72–1.41)	80173	121	1.36 (1.13–1.63)	70	191	1.00 (0.82–1.22)
Crohn's disease	208407	78	1.58 (1.25–1.97)	58	172	0.90 (0.69–1.18)	183916	74	1.19 (0.93–1.49)	63	58	1.17 (0.92–1.49)
Discoid lupus erythematosus	9891	17	4.21 (2.45–6.76)	15	26	1.16 (0.70–1.92)	3005	14	5.51 (3.00–9.27)	10	17	1.28 (0.74–2.20)
Graves' disease/hypothyroidism	455932	230	1.30 (1.14–1.48)	188	376	1.00 (0.86–1.16)	85263	100	1.43 (1.16–1.73)	71	112	0.93 (0.75–1.15)
Hashimoto's disease/hypothyroidism	96639	44	1.01 (0.73–1.35)	32	111	0.90 (0.64–1.26)	24110	31	1.59 (1.08–2.26)	21	32	0.86 (0.56–1.32)
Immune thrombocytopaenic purpura	22976	10	2.02 (0.96–3.73)	8	8	0.81 (0.31–2.16)	21268	9	1.56 (0.71–2.97)	4	16	0.54 (0.23–1.30)
Localised scleroderma	9546	10	2.09 (0.99–3.85)	9	6	1.67 (0.87–3.21)	2273	2	1.34 (0.13–4.92)	2	1	2.13 (0.55–8.34)
Multiple sclerosis	121186	36	0.94 (0.66–1.30)	31	56	1.21 (0.82–1.77)	63848	35	0.96 (0.67–1.34)	26	41	1.37 (0.96–1.96)
Myasthenia gravis	20561	7	1.08 (0.43–2.23)	9	7	1.01 (0.46–2.26)	12109	11	1.02 (0.50–1.82)	12	31	0.70 (0.35–1.39)
Pernicious anaemia	36200	14	0.70 (0.38–1.18)	13	3	2.21 (1.19–4.11)	30922	31	0.711 (0.48–1.00)	31	26	1.03 (0.70–1.52)
Polymyalgia rheumatica	162276	102	1.04 (0.85–1.27)	83	159	1.04 (0.84–1.29)	90846	100	1.05 (0.86–1.28)	90	110	0.99 (0.79–1.24)
Polymyositis/dermatomyositis	14546	26	4.65 (3.03–6.82)	22	33	0.76 (0.47–1.22)	9512	26	3.83 (2.50–5.61)	22	11	1.72 (1.15–2.56)
Primary biliary cirrhosis	10588	9	1.36 (0.62–2.59)	8	8	1.34 (0.64–2.82)	2440	4	1.75 (0.45–4.52)	3	14	0.54 (0.17–1.66)
Psoriasis	140958	89	1.72 (1.38–2.11)	67	130	1.00 (0.78–1.27)	135049	135	1.50 (1.26–1.78)	86	149	1.04 (0.86–1.26)
Rheumatic fever	20262	14	1.95 (1.06–3.29)	12	23	0.65 (0.34–1.25)	57145	62	2.10 (1.61–2.70)	46	100	0.79 (0.60–1.04)
Rheumatoid arthritis	528646	330	1.30 (1.17–1.45)	234	436	0.97 (0.86–1.10)	203439	343	1.67 (1.50–1.86)	275	360	1.15 (1.02–1.29)
Sarcoidosis	87991	43	1.20 (0.87–1.62)	39	61	1.25 (0.89–1.75)	89833	61	1.37 (1.05–1.76)	51	91	1.17 (0.89–1.53)
Systemic lupus erythematosus	72010	51	2.18 (1.62–2.87)	53	54	1.33 (0.99–1.79)	14630	34	3.08 (2.13–4.31)	20	33	1.09 (0.76–1.58)
Systemic sclerosis	41971	39	2.65 (1.89–3.63)	25	47	1.15 (0.80–1.67)	48052	49	1.93 (1.43–2.55)	36	61	1.08 (0.80–1.46)
Ulcerative colitis	225062	55	0.94 (0.71–1.22)	41	119	0.97 (0.72–1.32)	261738	100	0.92 (0.75–1.12)	70	180	0.79 (0.63–1.00)
Granulomatosis with polyangiitis	79454	37	0.80 (0.56–1.11)	32	30	1.13 (0.79–1.62)	36331	64	1.21 (0.93–1.55)	58	55	1.08 (0.83–1.42)
All	2867852	1349	1.29 (1.22–1.36)	1056	2026	1.01 (0.94–1.07)	1910778	1522	1.36 (1.30–1.43)	1139	1837	1.03 (0.97–1.09)

Data are presented as n, unless otherwise specified. Bold indicates that the 95% CI does not include 1.00.

TABLE 3 Standardised incidence ratios (SIRs) and hazard ratios (HRs) for lung cancer after a specified autoimmune disease by histology

Autoimmune disease	Adenocarcinoma					Squamous cell carcinoma					Large cell carcinoma					Small cell carcinoma				
	Observed	SIR (95% CI)	Deaths	Person-ys	HR (95% CI)	Observed	SIR (95% CI)	Deaths	Person-ys	HR (95% CI)	Observed	SIR (95% CI)	Deaths	Person-ys	HR (95% CI)	Observed	SIR (95% CI)	Deaths	Person-ys	HR (95% CI)
Addison's disease	5	1.17 (0.37-2.74)	4	10	1.19 (0.44-3.16)	7	1.98 (0.79-4.11)	6	3	2.00 (0.90-4.46)	4	1.28 (0.34-3.35)	4	1	2.22 (0.83-5.91)	2	1.08 (0.10-3.96)	2	5	0.44 (0.11-1.78)
Amorphous lateral sclerosis	2	0.49 (0.05-1.81)	2	2	1.65 (0.41-6.59)	5	1.02 (0.32-2.40)	3	3	1.04 (0.33-3.21)	9	2.27 (1.03-4.32)	9	6	1.12 (0.58-2.14)	3	1.61 (0.30-4.76)	3	0.1	5.49 (1.77-17.05)
Ankylosing spondylitis	11	0.78 (0.39-1.39)	6	14	0.79 (0.35-1.75)	16	1.23 (0.70-2.01)	10	15	1.29 (0.69-2.39)	14	1.26 (0.69-2.13)	13	6	1.51 (0.88-2.61)	7	1.12 (0.44-2.31)	7	5	1.05 (0.50-2.20)
Behçet's disease	8	1.22 (0.52-2.42)	7	20	0.73 (0.35-1.54)	7	1.07 (0.42-2.21)	4	19	0.59 (0.22-1.56)	7	1.30 (0.51-2.69)	6	15	0.79 (0.35-1.76)	4	1.34 (0.35-3.47)	4	5	0.59 (0.22-1.57)
Celiac disease	5	0.83 (0.26-1.95)	0	8		8	1.72 (0.73-3.40)	6	40	0.48 (0.22-1.08)	5	1.19 (0.37-2.79)	3	6	0.57 (0.18-1.76)	3	1.15 (0.22-3.39)	3	3	0.62 (0.20-1.92)
Chronic rheumatic heart disease	32	0.99 (0.67-1.39)	24	76	1.05 (0.71-1.57)	55	1.46 (1.10-1.90)	43	78	0.98 (0.72-1.32)	26	0.86 (0.56-1.26)	20	53	0.77 (0.50-1.20)	25	1.63 (1.05-2.41)	25	9	1.70 (1.14-2.51)
Crohn's disease	46	1.31 (0.96-1.75)	34	99	0.97 (0.69-1.36)	35	1.43 (0.99-1.98)	28	59	1.06 (0.73-1.54)	28	1.20 (0.80-1.73)	26	17	1.28 (0.87-1.88)	22	1.51 (0.94-2.29)	21	12	1.16 (0.75-1.78)
Discoid lupus erythematosus	9	4.55 (2.05-8.67)	8	6	1.46 (0.73-2.92)	5	3.22 (1.02-7.58)	3	17	0.42 (0.14-1.31)	10	6.86 (3.27-12.66)	10	19	1.02 (0.55-1.89)	6	7.36 2.65-16.12	6	2	2.83 (1.28-6.28)
Graves' disease/hyperthyroidism	93	1.19 (0.96-1.46)	68	168	0.86 (0.68-1.10)	66	1.25 (0.97-1.59)	51	107	0.92 (0.70-1.21)	73	1.37 (1.07-1.72)	70	59	1.09 (0.87-1.38)	55	1.73 (1.30-2.25)	51	51	0.91 (0.69-1.20)
Hashimoto's disease/hypothyroidism	17	0.89 (0.52-1.43)	12	33	1.22 (0.70-2.16)	14	0.98 (0.54-1.65)	10	22	0.90 (0.49-1.68)	22	1.66 (1.04-2.52)	19	24	0.77 (0.49-1.20)	10	1.19 (0.57-2.20)	8	32	0.85 (0.33-1.30)
Immune thrombocytopenic purpura	7	2.14 (0.85-4.44)	4	6	0.72 (0.27-1.91)	3	1.23 (0.23-3.65)	0	0		3	1.34 (0.25-3.98)	2	11	0.62 (0.15-2.47)	3	2.19 (0.41-6.47)	3	1	2.67 (0.86-8.29)
Localised scleroderma	5	2.51 (0.79-5.91)	5	3	2.09 (0.87-5.00)	4	3.05 (0.79-7.88)	4	3	1.66 (0.62-4.43)	2	1.60 (0.15-5.88)	1	0.2	2.41 (0.34-17.11)	0				
Multiple sclerosis	23	1.00 (0.63-1.51)	17	16	1.54 (0.96-2.48)	16	0.96 (0.55-1.56)	12	20	1.11 (0.63-1.95)	15	0.90 (0.50-1.50)	15	10	1.39 (0.84-2.30)	7	0.75 (0.30-1.54)	7	2	2.22 (1.06-4.65)
Myasthenia gravis	2	0.41 (0.04-1.52)	1	6	0.43 (0.06-3.05)	3	0.67 (0.19-2.00)	1	21	0.22 (0.03-1.53)	7	1.92 (0.76-3.99)	7	4	1.56 (0.74-3.28)	5	2.28 (0.72-5.37)	5	6	0.64 (0.27-1.54)
Pericardial aneurysm	6	0.40 (0.14-0.88)	2	0.3	2.15 (0.54-8.52)	11	0.59 (0.29-1.05)	8	19	0.66 (0.33-1.32)	12	0.83 (0.42-1.45)	11	5	1.34 (0.74-2.43)	7	0.94 (0.37-1.96)	7	4	0.87 (0.42-1.83)
Polymyalgia rheumatic	63	1.14 (0.87-1.45)	50	128	0.95 (0.72-1.26)	46	0.98 (0.72-1.30)	38	63	1.12 (0.82-1.54)	41	1.06 (0.76-1.44)	38	17	1.51 (1.10-2.07)	26	1.00 (0.65-1.47)	21	30	0.67 (0.44-1.03)
Polymyositis/dermatomyositis	13	3.68 (1.95-6.31)	10	13	1.03 (0.56-1.92)	12	3.94 (2.02-6.90)	9	8	0.99 (0.51-1.90)	15	5.56 (3.10-9.19)	13	13	1.36 (0.79-2.34)	7	4.53 (1.79-9.38)	6	6	1.02 (0.46-2.27)
Primary biliary cirrhosis	1	0.33 (0.00-1.91)	0	0		9	5.10 (2.31-9.73)	7	21	0.72 (0.34-1.51)	1	0.58 (0.00-3.32)	1	0.2	4.67 (0.67-32.63)	1	0.77 (0.00-4.40)	1	0.2	2.65 (0.37-18.88)
Psoriasis	48	1.23 (0.91-1.63)	29	90	0.73 (0.50-1.05)	63	1.71 (1.31-2.19)	53	78	1.05 (0.80-1.38)	49	1.58 (1.17-2.09)	42	19	1.39 (1.02-1.88)	35	2.00 (1.39-2.79)	32	20	1.21 (0.86-1.72)
Rheumatic fever	24	2.55 (1.63-3.80)	17	50	0.65 (0.41-1.05)	21	2.06 (1.28-3.16)	17	38	0.79 (0.49-1.27)	8	0.99 (0.42-1.96)	7	7	0.84 (0.40-1.76)	7	1.60 (0.63-3.31)	7	8	0.74 (0.35-1.54)
Rheumatoid arthritis	152	1.17 (0.99-1.37)	121	185	1.05 (0.88-1.26)	192	1.71 (1.48-1.97)	153	318	0.97 (0.83-1.14)	143	1.41 (1.19-1.67)	121	102	1.11 (0.93-1.33)	91	1.60 (1.29-1.97)	85	85	1.06 (0.86-1.32)
Sarcoidosis	28	1.19 (0.79-1.72)	23	33	1.35 (0.90-2.03)	21	1.10 (0.68-1.69)	18	60	0.97 (0.61-1.54)	20	1.15 (0.70-1.77)	19	11	1.50 (0.96-2.36)	15	1.49 (0.83-2.46)	14	11	1.10 (0.65-1.86)
Systemic lupus erythematosus	23	2.12 (1.34-3.18)	21	20	1.32 (0.86-2.03)	22	2.97 (1.86-4.50)	16	37	0.92 (0.56-1.50)	19	2.55 (1.53-3.99)	18	13	0.99 (0.62-1.57)	15	3.38 (1.89-5.59)	15	6	2.25 (1.36-3.74)
Systemic sclerosis	32	2.98 (2.03-4.21)	23	44	1.15 (0.76-1.73)	27	2.54 (1.68-3.71)	25	43	1.19 (0.80-1.76)	12	1.36 (0.70-2.38)	9	8	0.88 (0.46-1.69)	8	1.63 (0.70-3.23)	5	9	0.87 (0.36-2.06)
Ulcerative colitis	49	0.99 (0.73-1.30)	40	95	1.09 (0.80-1.49)	34	0.85 (0.59-1.20)	28	99	0.75 (0.52-1.09)	32	0.90 (0.62-1.28)	28	30	0.97 (0.67-1.40)	18	0.84 (0.50-1.33)	14	26	0.88 (0.52-1.50)
Granulomatosis with polyangiitis	22	0.88 (0.55-1.34)	17	15	1.10 (0.68-1.76)	32	1.16 (0.80-1.64)	26	36	1.09 (0.74-1.60)	30	1.37 (0.92-1.96)	25	14	1.24 (0.84-1.83)	6	0.51 (0.18-1.12)	6	2	2.09 (0.94-4.67)
All	741	1.20 (1.11-1.28)	557	1153	0.99 (0.91-1.08)	740	1.40 (1.30-1.50)	582	1240	0.94 (0.86-1.02)	615	1.31 (1.21-1.42)	544	475	1.13 (1.04-1.23)	388	1.43 (1.29-1.58)	357	348	1.03 (0.93-1.15)

Data are presented as n, unless otherwise specified. Bold indicates that the 95% CI does not include 1.00.

could be ascribed merely to smoking. Smoking is a known 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 [29]. We adjusted the data for COPD which is, of course, not optimal, but the only available means, together with socioeconomic status, to control for the possible bias due to differential smoking habits. However, to explain, even without any adjustments, the observed differences by smoking habit would require an extreme segregation of smoking behaviour [30]. In addition, the practically identical SIRs between males and females rule out strong effects of smoking because historically smoking prevalence has been higher among Swedish males compared to females and the female lung cancer incidence has not yet reached the male incidence [31]. A further point is that survival may be worse among smokers than nonsmokers, and the present overall HR was 1.02 [32, 33].

Interestingly, all autoimmune diseases that were associated with an SIR >2.0 are known to present with various kinds of lung manifestations. The highest risk was observed after discoid lupus erythematosus (4.71); generalised discoid lupus can affect the lungs and it can progress to systemic lupus erythematosus with common lung manifestations. The present SIR for systemic lupus erythematosus was 2.47. An excess in lung cancer has been observed in six small previous studies but no specific histology has been implicated [9, 10]. Herein we show that both discoid lupus erythematosus and systemic lupus erythematosus affect all lung cancer histologies, with the highest risk for small cell carcinoma. The present risk for lung cancer in systemic sclerosis patients was 2.19, somewhat higher than the 1.6 obtained in a Danish study applying a similar design as our study [34]. The localised form of the disease, localised scleroderma, showed a somewhat lower SIR but higher SMR. Both of these autoimmune diseases were approximately four times more common in females compared to males and the SIRs were also somewhat higher among females. Among other autoimmune diseases with lung manifestations, rheumatoid arthritis and sarcoidosis showed an increased risk of lung cancer, in agreement with previous studies [11, 14], whereas no increased risk was noted for Sjögren's syndrome or granulomatosis with polyangiitis [8]. The high risks of lung cancer in diseases that show local lung manifestations suggest that autoimmune lesions may help to drive lung cancer. Similarly, high risks of localised cancers have been described for Crohn's disease and ulcerative colitis [35, 36]. These data support the role of localised inflammation and related oxidative lesions in promoting cancer [37, 38]. Accordingly, lung cancer mortality is significantly reduced in clinical trials with daily intake of aspirin [39]. Although we cannot exclude the role of immunosuppressive therapy on lung cancer risk after some autoimmune diseases, there was no increase, for example, after myasthenia gravis for which immunosuppressive therapy may be applied for extended periods of time [40, 41].

The interpretation of the histology-specific analyses is complicated because of small numbers and changing trends in histology. It was, however, striking that the rarest histological type, small cell carcinoma, showed the highest SIR for discoid lupus erythematosus (7.36) and for the related systematic lupus (3.38). Small cell carcinoma showed also the highest

overall risks. Also of note was that among the 13 cases of lung cancers following primary biliary cirrhosis, nine were squamous cell carcinomas (SIR 5.10).

The data on survival showed that autoimmune disease has no large influence, implying that autoimmune disease does not limit treatment even for autoimmune diseases that have pulmonary manifestations, and that the autoimmune process does not facilitate lung cancer progression. One of the reasons may be the poor prognosis of lung cancer in itself. In our previous study, survival from seven digestive tract cancers was followed after autoimmune disease [20]. HRs were increased for many cancers with an intermediary prognosis but not for stomach cancer, which has a poor prognosis in itself. It is noteworthy in the present study that there were only four autoimmune disease cancer pairs for which both SIR and HR were increased and three of these included small cell carcinoma after chronic rheumatic heart disease, discoid lupus erythematosus and the related systematic lupus. As the principle treatment for small cell carcinoma is chemotherapy, compared to surgery for other types, it is conceivable that comorbidities are more treatment limiting when the treatment lasts for an extended period.

In conclusion, the present data showed an increase in SIR for lung cancer after 12 autoimmune diseases, SMR was increased after 11 autoimmune diseases and HR after two autoimmune diseases. All autoimmune diseases associated with an SIR >2.0 are known to present with lung manifestations, suggesting that the autoimmune process contributes to lung cancer susceptibility. Autoimmune disease did not influence survival overall but some autoimmune diseases appeared to impair survival in small cell carcinoma.

SUPPORT STATEMENT

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STATEMENT OF INTEREST

None declared.

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