



Effect of autoimmune diseases on risk and survival in female cancers

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HIGHLIGHTS

- We analyzed systematically risk and survival of female cancers in 200,000 patients diagnosed with 33 different autoimmune (AI) diseases.
- Breast, endometrial and ovarian cancers were decreased after all AI diseases and most changes after individual AIDs were decreased risks.
- For cervical and other genital cancers only increased risks were found.

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ABSTRACT

Objectives. Patients with autoimmune (AI) diseases are diagnosed with increased frequencies of some cancers, which may depend on the underlying dysregulation of the immune system or treatment. Data on female cancers are limited.

Methods. We analyzed systematically risk and survival of female cancers of the breast, uterus, ovary and other genital organs in close to 200,000 patients diagnosed with any of 33 different AI diseases. Standardized incidence ratios (SIRs) for risk and hazard ratios (HRs) for survival were calculated for subsequent incident cancers or cancer deaths up to year 2008.

Results. For all breast cancer after any AI diseases, the SIR was 0.94; SIRs were modestly increased after two AI diseases and decreased after nine AI diseases, including Sjogren syndrome (0.46). For cervical cancer, the risk was increased after discoid lupus erythematosus (3.34) and systemic sclerosis (2.43). The HR was 2.12 in chronic rheumatic heart disease patients. The overall SIR for endometrial cancer was 0.85, with low SIR in ankylosing spondylitis (0.37); the HR was 4.05 for Sjogren syndrome. The SIR for ovarian cancer was increased for polymyositis/dermatomyositis (3.26) while the HR was increased for multiple sclerosis (2.43). The overall SIR for other genital cancers was increased to 1.54 and a very high risk of 35.88 was observed in localized scleroderma.

Conclusions. Breast, endometrial and ovarian cancers were decreased after all AI diseases and most significant changes after individual AI diseases were towards lower risks. Probably treatment related factors explain the findings. For cervical and other genital cancers all significant changes were increased risks.

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Introduction

Autoimmune (AI) diseases are a heterogeneous group of diseases which jointly affect 5 to 10% of the population in developed countries [1]. AI diseases are characterized by aberrant attack of the immune system against own its antigens, either systemically or organ-specifically [2]. Many cancers are increased in AI disease patients but whether the mechanisms are related to the disturbances in the immune system or possibly to immunosuppressive therapies remain unknown [3–6]. The associations with AI diseases and lymphoma have been explained by

immune-related mechanistic links [3–6]. For solid tumors such links may be more complex but generally AI manifestations are found in organs where cancer risks are increased in AI patients [3–6]. AI diseases may influence cancer survival, like any co-morbidity, for example by worsening the general health condition of patients or by limiting therapeutic options [7,8].

Female cancers of the breast, uterus, ovary and genital organs are hormone sensitive and limited data are available on the possible modification of cancer risk at these sites in AI disease patients. Usually the published studies have addressed one particular AI disease and one or a few female cancers. For example for rheumatoid arthritis most studies suggest decreased or no risks in most female cancers [9–11]; in these patients, the survival in breast cancer has been favorable [12]. Similarly most female cancers were decreased in patients with systemic lupus erythematosus, with the exception of cervical

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cancer which appeared to be increased [13–15]. Sjogren syndrome has been associated with a risk of breast cancer but for autoimmune hypothyroidism the results have been controversial [16–18]. In the present study we examined risks of the five female cancer using standardized incidence ratio (SIR) and survival in these cancers using hazard ratio (HR) in patients who had been hospitalized for any of 33 AI diseases, covering the total Swedish population.

Material and methods

The analyses were accomplished by combining various Swedish national datasets as has been done in the previous study [6]. AI disease patients were identified from the Swedish Hospital Discharge Register that records complete data on all discharges with dates of hospitalization and diagnoses in some regions since 1964 and nation-wide after 1986. The International Classification of Diseases codes used were described earlier [19,20]. A total of 33 diseases were covered but we show only data for AI diseases when at least two cancers were recorded. Breast cancer had the most cases, but for chorea minor and Reiter disease less than two cases were recorded. However, none of the cancers with less than two cases following any AI diseases were significant. The 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.

Cancers were obtained from the nation-wide Swedish Cancer Registry. 'Other female genital cancer' included vagina, vulva (largest case numbers) and other parts. Person-years of follow-up were calculated from the date of discharge with the first main diagnosis of AI diseases until death, emigration, or closing date, December 31, 2008. SIRs were calculated as the ratio of observed (O) to expected number of female cancers. Expected numbers were calculated for anyone not hospitalized for any AI diseases. The expected numbers were calculated as age (5-year groups), sex, period (5-year groups), region and socioeconomic status-specific standard incidence rates. Additional adjustments were made for hospitalization for obesity using codes ICD7 = 287.00, 287.09; ICD8 = 277.99; ICD9 = 278A; ICD-10 = E65–E68 (26). Similar adjustments were made for hospitalization for chronic obstructive pulmonary disease (as a surrogate for smoking; codes: ICD7 = 500–502; ICD8 = 490–493; ICD9 = 490–496; ICD-10 = J40–J49) and alcoholism (codes: ICD9 = 303; ICD-10 = F10.1–F10.9). Additional adjustments were made for parity (0, 1, 2+) and age at first childbirth (<20, 20–29, 30+). Confidence intervals (95%CI) were calculated assuming a Poisson distribution. Cox regression analyses were used to estimate HRs, which could be interpreted as mortality rate ratio. Adjustments were done as above. The analyses were for deaths in female cancer while deaths from other causes were censored. 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.

Results

Table 1 shows SIR and HRs for the 4607 breast cancer patients after 31 AI diseases. Also are shown the total number of AI disease patients (199,466 women); the commonest AI disease was rheumatoid arthritis, diagnosed in 38,881 women. For all breast cancer after any AI diseases, the SIR was 0.94 and the HR was 0.95 (not significant). SIRs were modestly increased after two AI diseases, Graves disease/hyperthyroidism (SIR 1.13) and ulcerative colitis (1.12). SIRs were decreased after nine AI diseases, including Sjogren syndrome (0.46) and celiac disease (0.60), as well as common AI diseases, rheumatoid arthritis (0.84) and Hashimoto/hypothyroidism (0.78). The HR was increased for pernicious anemia (1.83) and decreased for psoriasis (0.68) and ulcerative

colitis (0.75). Notably, no consistent increases or decreases in SIR and HR were noted, and for pernicious anemia and ulcerative colitis the changes were in opposite directions. The last line in Table 1 shows data on all 5 cancers of the present study after any AI disease; the SIR was 0.94 but the HR was unchanged (0.99).

The database has no information on the duration of AI disease but we used as a surrogate of duration and severity, the number of hospitalizations for an AI diseases. Among all AI diseases, 56% were hospitalized once, 16% twice and 28% three or more times (3+). Separate analyses were carried out by the number of hospitalization but, with for the interest of space, we added only data on 3+ hospitalizations as the penultimate line to Table 1. The SIR for breast cancer after AI diseases with 3+ hospitalization changed minimally (0.97) but the HR was increased to 1.29. HR after rheumatoid arthritis was 2.10, and increased HRs were found also after multiple sclerosis (2.33), polymyositis/dermatomyositis (4.40) and systemic sclerosis (4.12).

For cervical cancer, the overall SIR and HR were unchanged (452 patients, Table 2). The risk was increased after discoid lupus erythematosus (3.34) and systemic sclerosis (2.33). The HR was 2.12 in chronic rheumatic heart disease patients. Analysis after 3+ hospitalizations increased the HR to 1.48 with a borderline significance, but the only AI disease after which the HR was increased was Crohn's disease (3 deaths, HR 5.31, 1.71–16.48).

Endometrial cancer was diagnosed in 943 patients, giving an overall SIR of 0.85 which was a significant decrease (Table 3). The risk was increased after one AI disease and decreased after three AI diseases. SIR was 4.11 in autoimmune hemolytic anemia patients. Ankylosing spondylitis patients had a low risk of 0.37, followed by rheumatoid arthritis (0.60) and Wegener granulomatosis (0.69). Only 99 cause-specific fatalities were identified, the HR was 4.05 for Sjogren syndrome and 1.51 for rheumatoid arthritis. Analysis after 3+ hospitalizations increased the HR to 1.88. Rheumatoid arthritis was the only individual AI disease after which the HR was increased (9 deaths, HR 3.36, 1.75–6.47).

Ovarian cancer was diagnosed in 741 AI disease patients, of whom as many as 422 had died (Table 4); however, the overall SIR was significantly decreased (0.90) while no change was noted for HR. The SIR was increased for polymyositis/dermatomyositis (3.26) while the HR was increased for multiple sclerosis (2.43). Analysis after 3+ hospitalizations increased both the SIR (1.33) and the HR (1.67). Table 4 shows the individual AI disease after which the HRs were increased; among these 8 AI diseases rheumatoid arthritis was associated with most ovarian cancer deaths.

Female genital cancer was diagnosed in only 252 AI disease patients but the overall SIR was increased to 1.54 (Table 5). The SIR was increased in 5 AI diseases. A very high risk of 35.88 was observed in localized scleroderma, but clear increases were also noted for systemic lupus (2.97), sarcoidosis (2.28), pernicious anemia (2.23) and Graves/hyperthyroidism (1.46). Only 82 persons had died and no HR was increased for a specific AI disease. Analysis after 3+ hospitalizations showed no change but the case numbers were very small.

Cancer survival depends on many parameters, including the stage which can be measured by the tumor (T)–node(N)–metastasis (M) classification [21]. Unfortunately, the TNM classification was only available for breast cancer since 2002. We compared the distribution of each T, N and M class between breast cancers following a specific AI disease to breast cancers unrelated to AI disease (data not shown). There were few significant differences overall, and only for pernicious anemia with an increased HR (1.83 from Table 1) was the T distribution different between AI disease related breast cancer and other breast cancer. However, the T class was lower among pernicious anemia patients, opposite to the expectation ($p < 0.0001$).

Discussion

The results on subsequent cancers after AI diseases on almost 200,000 women were heterogeneous and there was only one AI disease

Table 1
SIRs and HRs for female breast cancer after a specified AI disease.

Autoimmune disease (case number)	Pyr	O	SIR	95%CI	Pyr	Deaths	HR	95% CI	With 3+ hospitalizations			
									Pyr	Deaths	HR	95%CI
Addison disease (1487)	33,114	22	0.64	0.40–0.97	171	4	0.89	0.33–2.36	18	1	1.78	0.25–12.65
Amyotrophic lateral sclerosis (2610)	27,822	11	0.59	0.29–1.06	73	2	1.08	0.27–4.32	4	1	5.32	0.75–37.60
Ankylosing spondylitis (1798)	112,824	59	1.04	0.79–1.35	438	7	0.58	0.27–1.21	28	0		
Autoimmune hemolytic anemia (536)	9332	4	0.47	0.12–1.21	52	1	0.67	0.10–4.77	2	0		
Behcet disease (1071)	63,182	31	1.07	0.73–1.52	266	8	1.13	0.57–2.26	4	1	7.01	0.99–49.57
Celiac disease (6549)	216,247	29	0.60	0.40–0.86	193	2	0.38	0.09–1.50	18	0		
Chronic rheumatic heart disease (7832)	16,6242	212	1.10	0.96–1.26	1491	40	0.87	0.64–1.18	474	10	0.72	0.39–1.34
Crohn's disease (12,886)	392,264	228	0.85	0.75–0.97	1728	38	0.83	0.61–1.14	398	13	1.17	0.68–2.02
Diabetes mellitus type I (10,651)	372,968	39	1.07	0.76–1.47	183	7	1.44	0.69–3.02	36	3	3.07	0.99–9.49
Discoid lupus erythematosus (568)	12,892	11	0.59	0.30–1.07	92	1	0.40	0.06–2.82	22	0		
Graves/hyperthyroidism (28,704)	541,104	972	1.13	1.06–1.21	7516	211	0.98	0.86–1.13	756	27	1.27	0.87–1.85
Hashimoto/hypothyroidism (7571)	120,705	148	0.78	0.66–0.91	1110	29	0.92	0.64–1.33	62	1	0.39	0.06–2.79
Immune thrombocytopenic purpura (2078)	44,220	20	0.87	0.53–1.35	89	2	0.72	0.18–2.88	8	1	3.73	0.56–25.00
Localized scleroderma (708)	11,817	16	0.76	0.44–1.24	154	2	0.47	0.12–1.87				
Lupoid hepatitis (278)	3740	4	1.05	0.27–2.73	9	0						
Multiple sclerosis (8486)	185,014	223	1.05	0.92–1.20	1317	40	1.04	0.76–1.42	154	12	2.33	1.32–4.11
Myasthenia gravis (1492)	32,648	28	0.87	0.58–1.26	144	3	0.66	0.21–2.03	23	1	1.52	0.21–10.76
Pernicious anemia (2994)	67,096	67	0.73	0.57–0.93	371	22	1.83	1.21–2.78	9	0		
Polyarteritis nodosa (583)	12,395	8	0.66	0.28–1.31	51	1	0.58	0.08–4.13	16	1	1.65	0.23–11.73
Polymyalgia rheumatica (14,376)	253,046	328	0.86	0.77–0.96	2174	62	1.00	0.78–1.29	76	3	1.58	0.51–4.89
Polymyositis/dermatomyositis (1264)	24,041	27	1.03	0.68–1.51	154	7	1.50	0.72–3.15	13	2	4.40	1.13–17.06
Primary biliary cirrhosis (1313)	13,020	22	0.81	0.51–1.23	85	4	1.47	0.55–3.90	17	1	1.55	0.22–11.04
Psoriasis (8162)	275,971	258	1.09	0.96–1.23	2008	38	0.68	0.50–0.94	287	5	0.70	0.29–1.67
Rheumatic fever (1091)	77,388	25	0.75	0.48–1.10	228	3	0.48	0.15–1.48	10	1	3.56	0.51–24.70
Rheumatoid arthritis (38,881)	731,954	957	0.84	0.79–0.89	6558	217	1.09	0.95–1.24	789	54	2.10	1.61–2.74
Sarcoidosis (5149)	177,765	155	0.92	0.78–1.08	1299	29	0.81	0.57–1.17	82	1	0.38	0.05–2.68
Sjögren syndrome (1516)	16,700	16	0.46	0.26–0.75	99	4	1.44	0.54–3.82	12	1	2.27	0.32–16.08
Systemic lupus erythematosus (5353)	86,627	103	0.87	0.71–1.06	661	23	1.21	0.81–1.82	125	4	1.06	0.40–2.83
Systemic sclerosis (3089)	89,997	72	1.03	0.81–1.30	461	13	0.92	0.53–1.58	40	6	4.12	1.87–9.06
Ulcerative colitis (14,272)	486,704	352	1.12	1.01–1.24	2849	56	0.75	0.58–0.98	700	11	0.59	0.33–1.07
Wegener granulomatosis (6076)	115,746	159	0.78	0.67–0.91	1058	46	1.30	0.97–1.74	44	0		
All (199,466)	4,777,665	4607	0.94	0.91–0.97	33,084	922	0.95	0.89–1.02	4230	161	1.29	1.10–1.51
All with 3+ hospitalizations	781,949	740	0.97	0.90–1.05	4230	161	1.29	1.10–1.51				
All for all 5 female cancers	4,777,665	6995	0.94	0.92–0.96	48,145	1712	0.99	0.94–1.04				

Bold type indicates that the 95% CI does not include 1.00.

Abbreviations: Pyr, person-years; O, observed; SIR, standardized incidence ratio; CI, confidence interval; HR, hazard ratio.

Table 2
SIRs and HRs for cervical cancer after a specified AI disease.

Autoimmune disease	Pyr	O	SIR	95%CI	Pyr	Deaths	HR	95%CI
Addison disease	33,114	5	1.67	0.53–3.92	29	2	1.10	0.28–4.41
Amyotrophic lateral sclerosis	27,822	2	1.30	0.12–4.78	21	0		
Ankylosing spondylitis	112,824	7	1.34	0.53–2.78	45	2	0.77	0.19–3.08
Celiac disease	216,247	3	0.58	0.11–1.72	9	1	1.84	0.26–13.06
Chronic rheumatic heart disease	166,242	20	1.18	0.72–1.82	153	12	2.12	1.20–3.74
Crohn's disease	392,264	26	0.89	0.58–1.31	205	4	0.85	0.32–2.26
Diabetes mellitus type I	372,968	8	0.71	0.30–1.41	126	0		
Discoid lupus erythematosus	12,892	6	3.34	1.20–7.32	92	1	0.46	0.07–3.27
Graves/hyperthyroidism	541,104	72	0.93	0.72–1.17	655	14	0.70	0.41–1.18
Hashimoto/hypothyroidism	120,705	13	0.84	0.44–1.44	89	4	0.96	0.36–2.56
Immune thrombocytopenic purpura	44,220	2	0.93	0.09–3.40	8	0		
Multiple sclerosis	185,014	18	0.92	0.54–1.45	77	8	1.81	0.91–3.62
Myasthenia gravis	32,648	3	0.99	0.19–2.93	22	1	1.10	0.15–7.80
Pernicious anemia	67,096	7	1.00	0.39–2.06	45	1	0.42	0.06–2.98
Polyarteritis nodosa	12,395	2	1.98	0.19–7.27	2	0		
Polymyalgia rheumatica	253,046	26	0.96	0.62–1.40	177	11	1.29	0.71–2.33
Polymyositis/dermatomyositis	24,041	3	1.37	0.26–4.06	15	0		
Psoriasis	275,971	26	1.16	0.76–1.70	203	11	1.28	0.71–2.31
Rheumatic fever	77,388	4	1.25	0.32–3.22	64	0		
Rheumatoid arthritis	731,954	105	1.12	0.92–1.36	773	35	1.03	0.74–1.44
Sarcoidosis	177,765	17	1.12	0.65–1.80	198	1	0.19	0.03–1.34
Sjögren syndrome	16,700	2	0.83	0.08–3.06	2	1	4.54	0.64–31.94
Systemic lupus erythematosus	86,627	16	1.39	0.79–2.27	191	1	0.25	0.04–1.75
Systemic sclerosis	89,997	14	2.33	1.27–3.93	88	3	0.73	0.24–2.27
Ulcerative colitis	486,704	31	0.98	0.67–1.40	302	4	0.60	0.22–1.59
Wegener granulomatosis	115,746	14	0.88	0.48–1.48	109	5	1.01	0.42–2.43
All	4,777,665	452	1.03	0.94–1.13	3640	122	0.91	0.76–1.09
All with 3+ hospitalizations	781,949	66	1.09	0.84–1.38	280	22	1.48	0.97–2.24

Bold type indicates that the 95% CI does not include 1.00.

Abbreviations: Pyr, person-years; O, observed; SIR, standardized incidence ratio; CI, confidence interval; HR, hazard ratio.

Table 3

SIRs and HRs for endometrial cancer after a specified AI disease.

Autoimmune disease	Pyrs	O	SIR	95%CI	Pyrs	Deaths	HR	95%CI
Addison disease	33,114	4	0.54	0.14–1.40	26	0		
Amyotrophic lateral sclerosis	27,822	5	1.12	0.35–2.63	26	0		
Ankylosing spondylitis	112,824	4	0.37	0.10–0.95	38	1	3.49	0.49–24.80
Autoimmune hemolytic anemia	9332	8	4.11	1.76–8.14	49	0		
Behcet disease	63,182	4	0.67	0.17–1.73	32	1	5.35	0.75–38.03
Celiac disease	216,247	5	0.51	0.16–1.19	41	0		
Chronic rheumatic heart disease	166,242	62	1.28	0.98–1.65	514	4	0.60	0.23–1.61
Crohn's disease	392,264	35	0.75	0.52–1.04	217	2	0.95	0.24–3.78
Diabetes mellitus type I	372,968	2	0.84	0.08–3.08	17	0		
Discoid lupus erythematosus	12,892	6	1.47	0.53–3.23	106	1	1.94	0.27–13.78
Graves/hyperthyroidism	541,104	182	0.96	0.82–1.10	1424	17	1.00	0.62–1.61
Hashimoto/hypothyroidism	120,705	49	1.05	0.77–1.38	420	3	0.55	0.18–1.71
Immune thrombocytopenic purpura	44,220	4	0.83	0.22–2.14	22	1	1.65	0.23–11.69
Localized scleroderma	11,817	8	1.53	0.65–3.02	25	1	1.05	0.15–7.49
Multiple sclerosis	185,014	55	1.29	0.97–1.68	395	8	1.91	0.95–3.82
Myasthenia gravis	32,648	10	1.55	0.74–2.87	73	2	2.06	0.51–8.23
Pernicious anemia	67,096	20	0.90	0.55–1.40	121	2	0.75	0.19–2.99
Polyarteritis nodosa	12,395	2	0.71	0.07–2.62	4	0		
Polymyalgia rheumatica	253,046	82	0.84	0.67–1.04	537	8	0.93	0.47–1.86
Polymyositis/dermatomyositis	24,041	4	0.67	0.17–1.74	21	1	3.89	0.55–27.65
Primary biliary cirrhosis	13,020	6	0.93	0.34–2.04	33	1	2.10	0.30–14.95
Psoriasis	275,971	40	0.76	0.54–1.03	388	1	0.33	0.05–2.36
Rheumatic fever	77,388	10	1.39	0.66–2.56	78	0		
Rheumatoid arthritis	731,954	168	0.60	0.52–0.70	1259	25	1.51	1.02–2.24
Sarcoidosis	177,765	38	0.99	0.70–1.36	303	5	1.33	0.55–3.20
Sjögren syndrome	16,700	6	0.72	0.26–1.58	30	2	4.05	1.01–16.22
Systemic lupus erythematosus	86,627	19	0.76	0.46–1.19	143	3	2.14	0.69–6.64
Systemic sclerosis	89,997	11	0.70	0.35–1.25	57	2	2.28	0.57–9.14
Ulcerative colitis	486,704	61	1.05	0.81–1.35	369	4	0.90	0.34–2.40
Wegener granulomatosis	115,746	34	0.69	0.48–0.96	238	4	0.75	0.28–2.01
All	4,777,665	943	0.85	0.80–0.91	6961	99	1.08	0.88–1.32
All with 3+ hospitalizations	781,949	141	0.82	0.69–0.97	772	22	1.88	1.24–2.86

Bold type indicates that the 95% CI does not include 1.00.

Abbreviations: Pyrs, person-years; O, observed; SIR, standardized incidence ratio; CI, confidence interval; HR, hazard ratio.

Table 4

SIRs and HRs for ovarian cancer after a specified AI disease.

Autoimmune disease	Pyrs	O	SIR	95%CI	Pyrs	Deaths	HR	95%CI	With 3+ hospitalizations			
									Pyrs	Deaths	HR	95%CI
Addison disease	33,114	5	0.91	0.29–2.15	25	1	0.49	0.07–3.45				
Ankylosing spondylitis	112,824	8	0.94	0.40–1.85	46	4	1.25	0.47–3.34	7	1	0.95	0.13–6.77
Autoimmune hemolytic anemia	9332	3	2.01	0.38–5.94	7	3	2.30	0.75–7.09				
Behcet disease	63,182	6	1.25	0.45–2.74	17	4	1.22	0.46–3.26				
Celiac disease	216,247	7	0.86	0.34–1.79	35	2	0.67	0.17–2.69	1	1	3.38	0.48–23.57
Chronic rheumatic heart disease	166,242	37	1.02	0.72–1.41	110	19	0.91	0.58–1.43	30	4	0.67	0.25–1.79
Crohn's disease	392,264	38	0.98	0.69–1.34	210	16	1.07	0.66–1.75	17	6	2.53	1.14–5.64
Diabetes mellitus type I	372,968	6	0.90	0.32–1.97	22	1	0.48	0.07–3.39				
Discoid lupus erythematosus	12,892	2	0.64	0.06–2.34	2	1	0.99	0.14–7.00				
Graves/hyperthyroidism	541,104	146	1.02	0.87–1.21	686	87	1.07	0.87–1.33	77	12	1.27	0.72–2.24
Hashimoto/hypothyroidism	120,705	30	0.93	0.63–1.33	100	20	1.48	0.95–2.29	13	2	1.54	0.39–6.17
Immune thrombocytopenic purpura	44,220	2	0.59	0.06–2.18	5	0						
Multiple sclerosis	185,014	24	0.70	0.45–1.04	96	20	2.43	1.56–3.77	16	9	3.50	1.82–6.73
Myasthenia gravis	32,648	5	1.01	0.32–2.38	27	3	1.67	0.54–5.17	3	1	1.62	0.23–11.50
Pernicious anemia	67,096	10	0.60	0.28–1.10	10	7	1.65	0.79–3.47	3	1	0.74	0.10–5.25
Polyarteritis nodosa	12,395	2	1.03	0.10–3.80	15	1	1.23	0.17–8.72				
Polymyalgia rheumatica	253,046	51	0.84	0.62–1.10	165	29	1.17	0.81–1.69	0	1	7.26	1.04–50.48
Polymyositis/dermatomyositis	24,041	14	3.26	1.77–5.48	77	10	1.43	0.77–2.66	6	4	3.41	1.28–9.09
Primary biliary cirrhosis	13,020	3	0.76	0.14–2.26	28	0			7	0		
Psoriasis	275,971	34	0.88	0.61–1.23	148	20	1.03	0.66–1.59	49	4	1.11	0.42–2.96
Rheumatic fever	77,388	2	0.36	0.03–1.32	8	0						
Rheumatoid arthritis	731,954	171	0.85	0.73–0.99	681	100	1.12	0.92–1.37	120	43	1.91	1.41–2.57
Sarcoidosis	177,765	32	1.14	0.78–1.61	191	17	0.95	0.59–1.52	2	3	3.62	1.18–11.13
Sjögren syndrome	16,700	2	0.38	0.04–1.40	6	0						
Systemic lupus erythematosus	86,627	19	0.96	0.58–1.51	89	12	1.07	0.61–1.88	9	0		
Systemic sclerosis	89,997	12	1.01	0.52–1.77	30	7	2.06	0.98–4.32	9	1	1.03	0.15–7.33
Ulcerative colitis	486,704	43	0.93	0.67–1.25	233	23	1.04	0.69–1.57	46	10	2.02	1.09–3.76
Wegener granulomatosis	115,746	25	0.66	0.42–0.97	139	15	0.77	0.47–1.28	0	1	9.66	1.36–68.52
All	4,777,665	741	0.90	0.84–0.97	3240	422	1.09	0.99–1.20	416	104	1.67	1.38–2.03
All with 3+ hospitalizations	781,949	157	1.33	1.13–1.55	416	104	1.67	1.38–2.03				

Bold type indicates that the 95% CI does not include 1.00.

Abbreviations: Pyrs, person-years; O, observed; SIR, standardized incidence ratio; CI, confidence interval; HR, hazard ratio.

Table 5
SIRs and HRs for the cancer of the other female genital after a specified AI disease.

Autoimmune disease	Pyrs	O	SIR	95%CI	Pyrs	Deaths	HR	95%CI
Addison disease	33,114	2	1.91	0.18–7.04	10	0		
Ankylosing spondylitis	112,824	3	2.18	0.41–6.44	11	1	0.94	0.13–6.66
Autoimmune hemolytic anemia	9332	2	6.39	0.60–23.50	2	0		
Celiac disease	216,247	2	1.40	0.13–5.15	10	1	0.91	0.13–6.48
Chronic rheumatic heart disease	166,242	13	1.74	0.92–2.99	42	5	1.22	0.51–2.93
Crohn's disease	392,264	10	1.52	0.72–2.81	54	2	0.72	0.18–2.86
Diabetes mellitus type I	372,968	3	4.24	0.80–12.54	22	0		
Graves/hyperthyroidism	541,104	40	1.46	1.04–1.98	192	16	1.21	0.74–1.98
Hashimoto/hypothyroidism	120,705	8	1.15	0.49–2.28	33	4	1.81	0.68–4.82
Immune thrombocytopenic purpura	44,220	2	2.81	0.27–10.34	7	1	6.91	0.97–49.37
Localized scleroderma	11,817	29	35.88	24.01–51.58	198	12	1.09	0.62–1.93
Multiple sclerosis	185,014	6	1.11	0.40–2.44	24	2	1.59	0.40–6.37
Myasthenia gravis	32,648	2	2.16	0.20–7.93	13	0		
Pernicious anemia	67,096	9	2.23	1.01–4.25	32	2	0.53	0.13–2.13
Polymyalgia rheumatica	253,046	17	1.14	0.66–1.83	76	4	0.77	0.29–2.07
Polymyositis/dermatomyositis	24,041	2	2.43	0.23–8.94	3	1	2.47	0.35–17.55
Psoriasis	275,971	10	1.34	0.64–2.47	60	2	0.72	0.18–2.88
Rheumatoid arthritis	731,954	33	0.81	0.55–1.13	136	8	0.78	0.39–1.57
Sarcoidosis	177,765	12	2.28	1.17–3.99	72	2	0.74	0.19–2.97
Systemic lupus erythematosus	86,627	10	2.97	1.41–5.48	48	3	1.61	0.52–5.00
Systemic sclerosis	89,997	6	2.56	0.92–5.62	28	1	0.77	0.11–5.44
Ulcerative colitis	486,704	13	1.60	0.85–2.74	70	5	1.52	0.63–3.66
Wegener granulomatosis	115,746	14	1.53	0.83–2.57	44	7	1.64	0.78–3.45
All	4,777,665	252	1.54	1.36–1.75	1220	82	1.07	0.86–1.34
All with 3+ hospitalizations	781,949	37	1.43	1.01–1.98	197	8	0.62	0.31–1.24

Bold type indicates that the 95% CI does not include 1.00.

Abbreviations: Pyrs, person-years; O, observed; SIR, standardized incidence ratio; CI, confidence interval; HR, hazard ratio.

(Graves/hyperthyroidism) after which two cancers were increased (breast and genital cancers) and only two AI diseases (rheumatoid arthritis and Wegener granulomatosis) after which three cancers were decreased (breast, endometrial and ovarian cancers in all cases); for HR, all changes related to individual AI diseases/cancers. A further heterogeneity was observed in opposite effects of AI disease on SIR and HR, which included pernicious anemia (breast cancer), ulcerative colitis (breast cancer) and rheumatoid arthritis (endometrial cancer); no concordant changes were observed. Although there are no compelling reasons to expect that SIR and HR change in the same direction, there are even less reasons to expect the opposite.

Breast, endometrial and ovarian cancers shared the decreased overall SIRs and these were the only cancers that were decreased after individual AI diseases. The clear exceptions were autoimmune hemolytic anemia which caused a large increase in endometrial cancer (SIR 4.11) and polymyositis/dermatomyositis which was associated with ovarian cancer (SIR 3.26). However, mechanisms for such increases are not clear and a chance association is possible as the study involved numerous comparisons. The mechanisms for the overall protective effects in breast, endometrial and ovarian cancers could be the interference in the gonadal steroid synthesis by immunosuppressive therapy, leading to earlier menopause [11,15]. In support of this mechanism was also the stronger protective effect observed for endometrial than for breast cancer, as endometrial cancer is thought to be most responsive to estrogens [22]. Another contributing option is the cancer protective effects of nonsteroidal anti-inflammatory drug therapies [23]. Protective effects of aspirin and other anti-inflammatory drug have been noted in some but not all studies on breast and endometrial cancers [24,25]. Although immunosuppressive therapy could have some protective effects in reducing the production of steroid hormones, no reduction was noted in some cancers following AI diseases for which immunosuppressive therapy is a standard treatment. For example, no cancer was decreased in myasthenia gravis patients who may receive immunosuppressive therapy for extended periods of time [26,27]. Previous studies have reported associations between autoimmune hypothyroidism and Sjogren syndrome with breast cancer risk [16,18]. Curiously, breast cancer risk was decreased after these AI diseases in the present study, and the decrease was highest among any AI disease

patients in Sjogren syndrome (SIR 0.47). In one study on hypothyroidism, no effects on breast cancer risk were found but the survival was improved [17].

Cervical and other genital cancers differ in pathophysiology from the other studied cancers in that human papillary virus (HPV) infections are dominant risk factors in these cancers [28]. The overall SIRs of these cancers were increased, although not significantly for cervical cancer. For individual AI diseases, only increased risks were noted; SIR was as high as 27 for genital cancer in localized scleroderma patients. Anal cancer shares the HPV etiology with other cancers. In our recent study, high anal cancer risks were observed after systemic lupus and sarcoidosis, both associated with increased risks of other genital cancers as shown here [6].

Some 28% of AI patients were hospitalized 3+ times and we showed data on this group of patients, assuming that their disease duration has been longer and more severe than for the other patients. The overall SIRs did not change for any of the studied cancers in this group of patients but the HRs became significant for all cancers, except for cervical cancer with a borderline significance and other female genital cancer with only 8 deaths. The HRs for rheumatoid arthritis patients with 3+ hospitalizations were commonly increased although the HRs were higher in some other AI disease patients. These data suggest that the survival disadvantage in AI disease patients is related to the chronic, severe disease, in line with other co-morbidities [7,8]. The analysis of TNM distributions of breast cancer in AI patients compared to other breast cancer patients showed no evidence for a more advanced stage in AI patients.

Some strengths of the present study include its large size, in a country of universal access to health care system of high standard. Diagnoses of AI disease, based on discharge data, are of high quality, as hospitalized 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 AI diseases, ranging from 74% for inflammatory bowel disease to 96% for rheumatoid arthritis [29]. Coverage is another issue, which depends, for example, on the severity of the condition, and some AI diseases rarely lead to hospitalization. The above review cited 42.5% for rheumatoid arthritis as an only AI

disease [29]. We have discussed coverage for AI diseases in many of our previous papers on familial clustering of AI diseases [30–33]. The Swedish Cancer Registry records all new cases of cancer and close to 100% of the cases are histologically or cytologically confirmed. The weakness of the present study was the unavailability of data on treatment and on some risk factors, such as age at menarche and menopause, breast feeding, oral contraception and hormone replacement therapy. For survival, also data on treatment and stage of disease in cancers other than breast would have been useful. Many comparisons were done and multiple comparisons are an issue for which internal and external consistency of the results and biological plausibility need to be considered. For SIR more than 150 basic comparisons were done, whereby the expected number of positive findings by chance would be 8 at $p = 0.05$; 27 positive results were found, suggesting that most are true findings. For HR, about 110 comparisons were done with at least 1 death; the 7 positive findings were slightly higher than the expected 5 or 6. It is however not clear if it is meaningful to count expected positive findings for rare events constituting most of HRs.

In summary, this is the largest study and the only one comparing systematically risk and survival in female cancers in AI disease patients. Breast, endometrial and ovarian cancers were decreased after combined AI diseases and most significant changes after individual AI diseases were towards lower risks. Probable treatment related factors explain the findings. For cervical and other genital cancers only increased risks were found, the highest SIR was for genital cancer in localized scleroderma patients.

Conflict of interest statement

The authors declare no conflict.

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