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Subsequent brain tumors in patients with autoimmune disease

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Background. Previous studies have reported increased risk of brain tumors after allergic conditions, but no systematic analyses of these tumors in patients with autoimmune disease (AId) have been performed. No data are available on survival among patients with AId from brain tumors. We analyzed systematically risks and survival in histological types of brain tumors among patients who received a diagnosis of 33 different AIds.

Patients and Methods. Standardized incidence ratios (SIRs) for brain tumors or hazard ratios (HRs) of deaths after brain tumors were calculated up to 2008 in 402 462 patients hospitalized for AId after 1964 and were compared with data on the population not hospitalized for AIds.

Results. Brain tumors were diagnosed in 880 patients with AId. No increased or decreased risks (SIRs) were noted for glioma, whereas the increased SIRs for meningioma after many AIds were likely to be attributable to surveillance bias. The data on survival showed overall decreases for glioma (HR, 1.15) and meningioma (HR, 1.26). The survival in both was decreased in patients with chronic rheumatic heart disease, multiple sclerosis, and rheumatoid arthritis. Overall, HRs were increased for glioma after 6 AIds and for meningioma after 7 AIds.

Conclusions. The present data showed that none of the 33 AIds influenced the risk of glioma. However, many AIds negatively influence survival in glioma and meningioma, probably through added physical burden or therapeutic limitations. Information of an existing AId in patients with newly diagnosed brain tumors should help the prognostic assessment and the design of treatment.

Keywords: comorbidity, glioma, hazard ratio, meningioma, standardized incidence ratio.

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Recent research has shown that immune cells and neuroimmune molecules, such as cytokines and chemokines, influence brain function in many ways. Similar to other parts of the body, the immune system protects the brain from infections but also causes autoimmune manifestations that may be related to many diseases of the nervous system, such as encephalitis, multiple sclerosis, Alzheimer disease, and some rare tumors.[1,2] However, there are very limited data on brain cancer risk among patients with autoimmune (AI) diseases (AIds), and the few studies on combined nervous system cancers in patients with AId from Sweden showed increased risks only in patients with psoriasis.[3–6] Even fewer studies are available relating to specific subtypes of brain tumors. According to meta-analyses of allergic conditions, glioma risk has been shown to be decreased in patients with asthma and eczema, whereas meningioma has been decreased primarily in patients with eczema.[7,8] The mechanisms underlying the reduced risks remain unclear, but it has been speculated that the hypersensitive immune system predisposing to asthma may be active against transformed cells. A recognized problem of interview studies on patients is the self-report bias of obtained data, and many studies did not verify asthma diagnosis reported by the cases and the controls. Although not all allergies are of AI origin, the protective effects would be opposite to the most common findings showing that AI conditions are usually associated with a risk of cancer.[9,10] When nervous system cancer risks were studied among patients who received a previous diagnosis of asthma, the standardized incidence ratio (SIR) was 1.29, and it was even higher (1.58) among those hospitalized for asthma >5 times, assumed to include severely ill patients.[11] These data cast some doubt on the protective effects reported in case-control studies.

In the present study, we report risks (SIRs) for brain tumor subtypes and survival after diagnosis (hazard ratio [HR]) among patients who have been admitted to

hospital for any of 33 AIds according to the nationwide Swedish Hospital Discharge Register. The study covers 402 462 patients with AId who presented with 880 subsequent brain cancers reported to the Swedish Cancer Registry.

Materials and Methods

The research database used in the present study was constructed from the national datasets at the Center for Primary Health Care Research, Lund University, Malmö, Sweden, that were also used in several previous studies on AIds and cancer.[12] The datasets were prepared by the health and population authorities, who use the individual national identification number for data linkage. Before release for research purposes, the authorities removed the personal number and replaced it with a serial number to provide anonymity. Patients with AId were identified from the Swedish Hospital Discharge Register, which records all discharges with dates of hospitalization and diagnoses, in some regions since 1964 and nationwide since 1986. The International Classification of Diseases codes for AIds used were described earlier.[13,14] A total of 33 diseases were covered. However, for statistical power, we present data for AIds for which at least 6 patients with brain cancer were recorded (see the first paragraph of Results).

Data on brain tumors were obtained from the nationwide Swedish Cancer Registry. Gliomas were analyzed in 2 groups: low grade (World Health Organization [WHO] grades I and II) and high grade (WHO grades III and IV). According to the available International Classification of Diseases (ICD) or histology codes, it was not possible to single out acoustic neurinoma. Lymphomas are listed under ICD codes for lymphoma, irrespective of location, and brain lymphomas cannot be singled out. Person-years of follow-up were calculated from date of discharge with the first main diagnosis of AId until diagnosis of cancer, death, emigration, or the closing date, 31 December 2008. SIRs were calculated as the ratio of observed to expected number of brain tumors. Expected numbers were calculated for anyone not hospitalized for AId (ie, essentially covering the Swedish population). The expected numbers were calculated by age (5-year groups), sex, period (5-year groups), region, and socioeconomic status–specific standard incidence rates. To control for potential confounding by obesity, smoking, alcohol consumption, and the related socioeconomic features, additional adjustments were made for hospitalization for obesity with use of codes ICD7 = 287.00, 287.09; ICD8 = 277.99; ICD9 = 278A; and ICD-10 = E65-E68. Similar adjustments were made for smoking with use of hospitalization for chronic obstructive pulmonary disease as a surrogate (codes: ICD7 = 500–502; ICD8 = 490–493; ICD9 = 490–496; and ICD-10 = J40-J49) and alcoholism (codes: ICD9 = 303; and ICD-10 = F10.1-F10.9). Ninety-five percent confidence intervals (CIs) were calculated assuming a Poisson distribution. The Cox regression analysis was used to estimate HRs. Adjustments were done as above. The analyses were for cause-specific deaths and overall deaths. 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

The total number of patients with AId was 402 462, who accumulated 4.78 million person-years at risk (ie, the mean follow-up time was 11.9 years) (Table 1). A total of 880 brain tumors were diagnosed, yielding a crude rate of 2.2 cases/1000 persons. Among the 33 AIds analyzed, 23 had >5 cases of brain cancer, and these are shown in the Tables. AIds not shown were autoimmune hemolytic anemia, chorea minor, discoid lupus, localized scleroderma, lupoid hepatitis, polyarteritis nodosa, polymyositis/dermatomyositis, primary biliary cirrhosis, Reiter disease, and Sjogren syndrome. These diseases were not significantly associated (neither SIR nor HR) with any brain tumors. In the present study, significance refers to nonoverlapping 95% CIs.

According to Table 1, all brain cancer was increased to an SIR of 1.20 after any AId (even including AIds not shown in Table 1). The SIR for brain tumor was increased after a total of 5 AIds, with the highest risks for Addison disease (2.19), multiple sclerosis (2.14), and systemic sclerosis (1.84). Of 880 patients with brain cancer, 600 died of any cause. In survival analysis, note that an HR >1.00 implies decreased survival. The overall survival was not changed among patients with AId, but survival was decreased for immune thrombocytopenic purpura (5.45), chronic rheumatic heart disease (1.79), and rheumatoid arthritis (1.20). We also assessed cause-specific survival with 270 deaths and somewhat decreased overall HR of 0.85; HRs were significantly decreased after some AIds, but case numbers were few. Survival was significantly decreased only among patients with immune thrombocytopenic purpura (5.22).

The SIR for all gliomas was unchanged, as it was for glioma after any AId (Table 1). The overall HR was increased to 1.15, and the HRs were increased after 6 AIds, including immune thrombocytopenic purpura (5.41), chronic rheumatic heart disease (4.70), type 1 diabetes (2.51), multiple sclerosis (2.30), polymyalgia rheumatica (1.60), and rheumatoid arthritis (1.47). For the 282 overall deaths, 230 were assigned to glioma, with an HR of 1.18. Significant HRs for overall survival among patients with specific AIds remained significant, and most were even higher for glioma-specific survival.

According to Table 2, the overall SIR for meningioma was 1.45, and the SIR was increased after 7 AIds—most for Addison disease (3.63), myasthenia gravis (3.57), and systemic sclerosis (3.11). The overall HR was 1.26, and increases were observed after 7 AIds—most for

Table 1. SIRs and HRs for brain cancer and glioma after a specified AId

Autoimmune disease	Pyrs for SIR	Brain cancer									Glioma								
		O	SIR	95%CI	Overall			Cause-specific			O	SIR	95%CI	Overall			Cause-specific		
					Deaths	HR	95%CI	Deaths	HR	95%CI				Deaths	HR	95%CI	Deaths	HR	95%CI
Addison disease (3010)	33 114	11	**2.19**	1.09–3.94	5	0.46	0.19–1.10	1	0.18	0.03–1.27	1	0.45	0.00–2.60	1	1.29	0.18–9.12	1	1.73	0.24–12.26
Amyotrophic lateral sclerosis (7623)	27 822	9	2.03	0.92–3.87	7	0.90	0.43–1.89	1	0.27	0.04–1.89	1	0.47	0.00–2.71	1	0.37	0.05–2.65	0		
Ankylosing spondylitis (6646)	112 824	23	1.35	0.85–2.03	16	1.10	0.67–1.79	11	1.15	0.64–2.08	15	1.70	0.95–2.81	14	0.77	0.46–1.30	10	0.69	0.37–1.29
Behcet disease (3874)	63 182	6	0.71	0.25–1.55	4	0.72	0.27–1.93	3	0.99	0.32–3.06	3	0.70	0.13–2.08	2	0.77	0.19–3.10	2	1.01	0.25–4.05
Celiac disease (11 459)	216 247	12	0.90	0.46–1.58	6	1.21	0.54–2.70	3	0.84	0.27–2.60	6	0.94	0.34–2.05	3	0.67	0.22–2.06	2	0.53	0.13–2.12
Chronic rheumatic heart disease (21 027)	166 242	38	1.09	0.77–1.50	34	**1.79**	1.28–2.51	11	1.20	0.67–2.18	12	0.76	0.39–1.34	12	**4.70**	2.66–8.28	8	**4.11**	2.06–8.21
Crohn disease (25 677)	392 264	47	0.98	0.72–1.31	24	0.91	0.61–1.35	17	1.00	0.62–1.61	24	1.07	0.68–1.59	17	0.70	0.43–1.12	14	0.69	0.41–1.16
Diabetes mellitus type I (22 801)	372 968	15	0.83	0.46–1.38	6	1.27	0.57–2.82	5	1.25	0.52–3.00	7	0.76	0.30–1.57	5	**2.51**	1.04–6.03	5	**2.98**	1.24–7.16
Graves/hyperthyroidism (42 020)	541 104	105	1.10	0.90–1.34	62	0.82	0.64–1.05	30	0.77	0.54–1.10	33	0.86	0.59–1.21	28	0.93	0.64–1.34	23	0.94	0.62–1.41
Hashimoto/ hypothyroidism (13 160)	120 705	34	**1.58**	1.09–2.21	22	1.01	0.66–1.53	10	0.86	0.46–1.60	12	1.41	0.73–2.48	11	0.82	0.46–1.49	9	0.85	0.44–1.63
Immune thrombocytopenic purpura (4324)	44 220	6	1.44	0.52–3.15	5	**5.45**	2.27–13.09	3	**5.22**	1.70–16.01	3	1.57	0.30–4.66	3	**5.41**	1.75–16.77	3	**7.46**	2.41–23.12
Multiple sclerosis (14 616)	185 014	64	**2.14**	1.65–2.73	41	1.07	0.79–1.45	19	0.84	0.54–1.32	20	1.49	0.91–2.31	19	**2.30**	1.47–3.61	18	**2.89**	1.82–4.59
Myasthenia gravis (3044)	32 648	7	1.38	0.55–2.85	3	0.47	0.15–1.47	1	0.27	0.04–1.89	1	0.45	0.00–2.57	1	3.49	0.49–24.82	1	4.63	0.66–32.75
Pernicious anemia (11 590)	67 096	22	1.44	0.90–2.18	19	0.97	0.62–1.51	2	**0.22**	0.05–0.86	2	0.30	0.03–1.12	2	0.44	0.11–1.75	1	0.26	0.04–1.85
Polymyalgia rheumatica (27 534)	253 046	67	**1.36**	1.06–1.73	54	1.15	0.88–1.50	24	1.03	0.69–1.54	26	1.27	0.83–1.86	26	**1.60**	1.09–2.35	20	**1.63**	1.05–2.52
Psoriasis (19 777)	275 971	50	1.15	0.85–1.52	32	0.84	0.60–1.19	21	1.02	0.66–1.56	18	0.90	0.53–1.43	17	1.22	0.76–1.97	16	1.48	0.90–2.41
Rheumatic fever (4306)	77 388	12	1.07	0.55–1.88	10	1.05	0.57–1.95	6	1.23	0.55–2.74	6	1.04	0.37–2.28	6	1.36	0.61–3.02	6	1.84	0.83–4.09
Rheumatoid arthritis (72 309)	731 954	158	1.10	0.93–1.28	119	**1.20**	1.01–1.44	44	0.86	0.64–1.16	52	0.86	0.64–1.13	47	**1.47**	1.10–1.96	39	**1.53**	1.12–2.10
Sarcoidosis (11 571)	177 765	36	1.24	0.87–1.72	25	1.25	0.84–1.85	14	1.26	0.75–2.13	19	1.41	0.85–2.20	17	1.03	0.64–1.65	12	0.89	0.51–1.58
Systemic lupus erythematosus (7624)	86 627	16	1.17	0.67–1.90	10	1.72	0.92–3.19	5	1.38	0.58–3.32	6	1.07	0.39–2.35	5	0.83	0.35–1.99	5	1.05	0.44–2.52

Systemic sclerosis (7169)	89 997	24	**1.84**	1.18–2.75	15	0.84	0.51–1.40	2	**0.21**	0.05–0.84	3	0.50	0.09–1.48	2	2.19	0.55–8.75	1	1.46	0.21–10.38
Ulcerative colitis (33 493)	486 704	65	1.02	0.79–1.31	39	1.06	0.77–1.45	24	1.04	0.69–1.55	32	1.05	0.72–1.48	27	1.06	0.73–1.55	22	1.06	0.70–1.61
Wegener granulomatosis (15 833)	115 746	36	1.31	0.92–1.82	30	0.98	0.68–1.40	6	**0.41**	0.19–0.92	10	0.91	0.43–1.68	10	1.32	0.71–2.45	6	1.03	0.46–2.28
All (402 462)	47 77 665	880	**1.20**	1.12–1.28	600	1.04	0.96–1.12	270	**0.85**	0.76–0.96	318	0.98	0.88–1.10	282	**1.15**	1.02–1.30	230	**1.18**	1.03–1.34

Bold type indicates that the 95% CI does not include 1.00.
Abbreviations: O, observed; Pyrs, person-years.

amyotrophic lateral sclerosis (7.66), systemic lupus (6.41), chronic rheumatic heart disease (2.40), and systemic sclerosis (2.02). Meningioma is a benign disease, and only 2 of 183 deaths were assigned to it (underlying cause of death stating meningioma and no contributing causes were listed). AIds did not change the overall SIR or HR of neurinoma. However, the SIR for neurinoma was increased to 6.57 among patients with systemic sclerosis. Of note, no significantly decreased risks were observed in Table 2.

There was a small group of other miscellaneous brain tumors (27 cases, 16 deaths) for which data are not shown. Among 4 tumors in patients with multiple sclerosis, 3 were hemangiomas or hemangioblastomas (SIR, 6.02; 95% CI, 1.14–17.82).

In Table 3, gliomas were analyzed in 2 groups: low grade (WHO grades I and II; 66 cases) and high grade (WHO grades III and IV; 251 cases). SIRs did not show significant changes for either type after any or all AIds. The overall survival after all AIds was 1.17 for both low- and high-grade gliomas, but it was significant only for high-grade disease, because of case numbers. HRs were significant for high-grade glioma after systemic lupus erythematosus (3.13) and systemic sclerosis (6.56), although these were not significant for all gliomas (Table 1). After multiple sclerosis, HR for low-grade glioma was higher than that for high-grade glioma, whereas the opposite was the case after type 1 diabetes and immune thrombocytopenic purpura, but the case numbers were few.

To follow changes in diagnostics and treatment, the analysis was separately performed during 2 periods (1964–1990 and 1991–2008). The periods were selected to allow a reasonable case number even for the latter, modern period. No difference for overall SIR was noted, whereas the overall HR slightly increased from 1.11 to 1.23 (Table 4). The changes in SIR were not significant for any individual AId (ie, 95% CIs overlapped); downward trends were observed for Addison disease and amyotrophic lateral sclerosis (only 2 cases for each in the latter period), whereas upward trends were noted for ankylosing spondylitis and Hashimoto/hypothyroidism. For HR, downward trends were observed for systemic lupus and ulcerative colitis, whereas the trends were upwards for amyotrophic lateral sclerosis and multiple sclerosis. Case numbers were small, except for multiple sclerosis and ulcerative colitis, for which the changes could be noted also for glioma-specific survival (data not shown). According to Table 4, the likelihood of brain cancer in patients with multiple sclerosis, compared to all other patients with AId, was 1.28 times higher in the latter period than in the former period. However, for the deaths, the ratio was 2.20 times higher.

We also performed sex-specific analyses, particularly because meningioma is predominantly a female disease; among the patients with meningioma, 86 were male and 262 were female. However, neither for meningioma nor for all brain cancer or other subtypes could we observe significant sex differences in SIR or HR (data not shown).

Table 2. SIRs and overall HRs for meningioma and neurinoma after a specified AId

Autoimmune disease	Menigioma						Neurinoma					
	O	SIR	95%CI	Deaths	HR	95%CI	O	SIR	95%CI	Deaths	HR	95%CI
Addison disease	6	**3.63**	1.31–7.96	3	0.89	0.29–2.77	2	5.33	0.50–19.61	0		
Amyotrophic lateral sclerosis	4	3.30	0.86–8.53	3	**7.66**	2.46–23.78	1	3.67	0.00–21.06	1	0.72	0.10–5.12
Ankylosing spondylitis	7	1.60	0.63–3.31	1	0.90	0.13–6.37	0					
Behcet disease	2	0.92	0.09–3.40	1	0.65	0.09–4.61	0					
Celiac disease	1	0.40	0.00–2.27	0			1	1.34	0.00–7.66	1	3.38	0.47–24.35
Chronic rheumatic heart disease	17	1.59	0.93–2.56	14	**2.40**	1.42–4.06	2	0.93	0.09–3.43	2	3.16	0.78–12.76
Crohn disease	13	0.90	0.48–1.55	3	1.78	0.57–5.52	4	0.99	0.26–2.55	0		
Diabetes mellitus type I	4	1.51	0.39–3.90	1	6.78	0.95–48.24	2	1.35	0.13–4.97	0		
Graves/hyperthyroidism	41	1.14	0.82–1.55	16	0.70	0.43–1.15	12	1.77	0.91–3.10	2	0.92	0.23–3.71
Hashimoto/hypothyroidism	14	1.75	0.95–2.94	7	1.35	0.64–2.85	1	0.73	0.00–4.16	0		
Immune thrombocytopenic purpura	1	0.87	0.00–4.99	1	2.87	0.40–20.40	1	3.58	0.00–20.54	0		
Multiple sclerosis	27	**2.68**	1.76–3.90	13	**1.84**	1.07–3.18	3	1.26	0.24–3.74	2	3.11	0.77–12.52
Myasthenia gravis	6	**3.57**	1.28–7.82	2	0.86	0.21–3.43	0					
Pernicious anemia	13	**2.65**	1.41–4.55	12	**1.79**	1.01–3.16	3	3.65	0.69–10.80	2	0.75	0.19–3.01
Polymyalgia rheumatica	26	1.52	0.99–2.23	15	1.04	0.63–1.73	0					
Psoriasis	17	1.27	0.74–2.03	8	0.74	0.37–1.49	5	1.58	0.50–3.72	0		
Rheumatic fever	3	1.08	0.20–3.20	2	1.05	0.26–4.22	0					
Rheumatoid arthritis	66	**1.31**	1.01–1.66	43	**1.58**	1.17–2.14	14	1.49	0.81–2.51	6	1.89	0.84–4.23
Sarcoidosis	11	1.24	0.61–2.22	3	0.48	0.15–1.48	2	0.89	0.08–3.27	1	**16.15**	2.24–116.70
Systemic lupus erythematosus	9	1.77	0.80–3.38	5	**6.41**	2.66–15.42	0					
Systemic sclerosis	12	**3.11**	1.60–5.45	10	**2.02**	1.09–3.77	6	**6.57**	2.36–14.38	0		
Ulcerative colitis	20	1.09	0.67–1.69	6	1.77	0.79–3.94	4	0.77	0.20–1.98	0		
Wegener granulomatosis	17	**1.78**	1.03–2.85	12	0.77	0.43–1.37	2	1.32	0.12–4.87	1	1.77	0.25–12.62
All	344	**1.45**	1.30–1.61	183	**1.26**	1.08–1.46	66	1.27	0.98–1.62	19	1.19	0.75–1.88

Bold type indicates that the 95% CI does not include 1.00.
Abbreviation: O, observed.

Table 3. SIRs and overall HRs for glioma after a specified AId

Autoimmune disease	Low grade glioma						High grade glioma					
	O	SIR	95%CI	Deaths	HR	95%CI	O	SIR	95%CI	Deaths	HR	95%CI
Addison disease	0						1	0.57	0.00–3.29	1	0.93	0.13–6.62
Amyotrophic lateral sclerosis	1	2.51	0.00–14.42	1	0.48	0.07–3.44	0					
Ankylosing spondylitis	2	1.14	0.11–4.19	2	0.86	0.21–3.43	12	1.71	0.88–2.99	12	0.84	0.47–1.47
Behcet disease	0						3	0.91	0.17–2.70	2	0.60	0.15–2.40
Celiac disease	3	0.97	0.18–2.86	0			3	0.92	0.17–2.72	3	0.68	0.22–2.12
Chronic rheumatic heart disease	4	1.71	0.45–4.43	4	**6.96**	2.60–18.67	8	0.60	0.26–1.19	8	**4.11**	2.05–8.24
Crohn disease	4	0.72	0.19–1.85	2	0.63	0.16–2.52	20	1.19	0.73–1.84	15	0.67	0.41–1.12
Diabetes mellitus type I	4	0.77	0.20–2.00	2	1.97	0.49–7.88	3	0.75	0.14–2.23	3	**18.97**	6.13–58.67
Graves/hyperthyroidism	8	1.14	0.49–2.26	5	0.82	0.34–1.97	25	0.80	0.52–1.19	23	1.01	0.67–1.52
Hashimoto/hypothyroidism	2	1.33	0.13–4.90	1	0.63	0.09–4.46	10	1.44	0.68–2.65	10	0.87	0.47–1.62
Immune thrombocytopenic purpura	1	1.72	0.00–9.88	1	2.83	0.40–19.96	2	1.52	0.14–5.58	2	**13.56**	3.40–54.14
Multiple sclerosis	5	1.88	0.59–4.42	5	**4.10**	1.70–9.84	15	1.40	0.78–2.32	14	**1.81**	1.07–3.07
Myasthenia gravis	0						1	0.56	0.00–3.20	1	2.78	0.39–19.73
Pernicious anemia	1	1.14	0.00–6.53	1	1.43	0.20–10.16	1	0.18	0.00–1.00	1	0.27	0.04–1.90
Polymyalgia rheumatica	4	1.29	0.34–3.35	4	2.11	0.79–5.63	22	1.26	0.79–1.92	22	**1.56**	1.03–2.37
Psoriasis	4	1.05	0.27–2.71	4	1.27	0.47–3.38	14	0.87	0.47–1.46	13	1.19	0.69–2.05
Rheumatic fever	1	0.84	0.00–4.79	1	0.90	0.13–6.38	5	1.10	0.35–2.58	5	1.63	0.68–3.91
Rheumatoid arthritis	6	0.63	0.23–1.39	4	2.08	0.78–5.57	46	0.91	0.66–1.21	43	1.32	0.98–1.79
Sarcoidosis	5	1.93	0.61–4.54	5	1.29	0.54–3.11	14	1.29	0.70–2.17	12	0.97	0.55–1.72
Systemic lupus erythematosus	2	1.74	0.16–6.41	1	0.42	0.06–3.01	4	0.90	0.23–2.33	4	**3.13**	1.18–8.34
Systemic sclerosis	1	0.78	0.00–4.45	0			2	0.43	0.04–1.57	2	**6.56**	1.64–26.21
Ulcerative colitis	5	0.71	0.22–1.67	1	0.26	0.04–1.84	27	1.16	0.76–1.69	26	1.23	0.83–1.80
Wegener granulomatosis	2	1.34	0.13–4.92	2	2.70	0.67–10.84	8	0.84	0.36–1.67	8	1.29	0.65–2.58
All	66	1.01	0.78–1.28	47	1.17	0.88–1.57	251	0.98	0.86–1.11	235	**1.17**	1.03–1.33

Bold type indicates that the 95% CI does not include 1.00.
Abbreviation: O, observed.

Table 4. SIRs and overall HRs for brain cancer after a specified AId by diagnostic periods

Autoimmune disease	1964–1990							1991–2008						
	Pyrs	O	SIR	95% CI	Deaths	HR	95% CI	Pyrs	O	SIR	95% CI	Deaths	HR	95% CI
Addison disease	10 427	7	**4.50**	1.78–9.33	2	0.37	0.09–1.48	9111	2	1.60	0.15–5.90	1	0.52	0.07–3.71
Amyotrophic lateral sclerosis	12 314	7	**3.43**	1.36–7.10	2	0.42	0.11–1.68	6272	2	1.54	0.15–5.67	2	**25.27**	6.36–100.46
Ankylosing spondylitis	39 322	6	1.24	0.44–2.71	5	1.26	0.52–3.02	16 856	8	**3.20**	1.37–6.33	5	1.27	0.53–3.05
Behcet disease	28 513	2	0.60	0.06–2.21	2	2.37	0.59–9.47	1926	1	4.88	0.00–27.97	0		
Celiac disease	54 491	3	0.90	0.17–2.68	1	1.94	0.27–13.77	47 587	5	1.79	0.57–4.22	4	1.40	0.53–3.72
Chronic rheumatic heart disease	85 701	24	1.31	0.84–1.95	20	**1.79**	1.16–2.79	24 440	6	1.27	0.46–2.79	4	1.27	0.48–3.37
Crohn disease	110 614	6	0.57	0.21–1.25	3	1.03	0.33–3.18	107 149	14	1.16	0.63–1.95	6	1.12	0.50–2.49
Diabetes mellitus type I	98 846	2	0.55	0.05–2.04	1	3.20	0.45–22.74	110 475	3	0.77	0.14–2.27	0		
Graves/hyperthyroidism	203 693	42	1.19	0.85–1.61	22	0.77	0.51–1.18	116 839	16	0.92	0.52–1.49	7	0.98	0.47–2.06
Hashimoto/hypothyroidism	43 501	10	1.25	0.59–2.31	7	1.04	0.50–2.19	28 195	15	**3.16**	1.77–5.23	8	1.09	0.54–2.18
Immune thrombocytopenic purpura	8640	1	1.49	0.00–8.56	1	11.37	1.63–79.27	24 703	5	2.16	0.68–5.07	4	**6.39**	2.40–17.02
Multiple sclerosis	67 706	28	**2.77**	1.84–4.01	13	0.87	0.50–1.49	48 076	20	**2.85**	1.74–4.40	13	**1.73**	1.01–2.98
Myasthenia gravis	10 430	0						9267	3	2.00	0.38–5.91	0		
Pernicious anemia	32 746	11	1.39	0.69–2.50	9	1.25	0.65–2.41	10 892	3	1.32	0.25–3.91	2	**1.23**	0.31–4.95
Polymyalgia rheumatica	72 444	22	**1.78**	1.11–2.70	17	1.50	0.93–2.41	68 969	22	1.46	0.91–2.21	16	**1.23**	0.75–2.01
Psoriasis	112 458	20	1.29	0.78–1.99	11	0.80	0.44–1.44	43 589	3	0.41	0.08–1.22	2	1.33	0.33–5.36
Rheumatic fever	34 274	7	1.60	0.64–3.32	2	0.38	0.09–1.51	3253	0					
Rheumatoid arthritis	304 697	72	1.17	0.92–1.48	50	1.24	0.94–1.63	165 591	28	0.90	0.60–1.30	15	**1.21**	0.73–2.01
Sarcoidosis	69 124	13	1.29	0.68–2.20	9	1.20	0.63–2.31	29 879	7	1.64	0.65–3.40	4	2.22	0.83–5.93
Systemic lupus erythematosus	31 854	6	1.24	0.45–2.72	6	**3.18**	1.43–7.09	22 065	5	1.55	0.49–3.65	2	1.41	0.35–5.65
Systemic sclerosis	36 494	12	**2.29**	1.18–4.02	7	0.82	0.39–1.73	8774	4	2.52	0.66–6.53	3	1.68	0.54–5.21
Ulcerative colitis	136 018	16	1.07	0.61–1.75	14	**2.10**	1.24–3.55	137 767	16	0.98	0.56–1.59	7	0.88	0.42–1.84
Wegener granulomatosis	61 898	20	1.26	0.77–1.95	16	1.43	0.87–2.33	9352	2	1.15	0.11–4.24	1	0.64	0.09–4.55
All	16 96 388	344	**1.32**	1.18–1.47	224	1.11	0.97–1.27	10 88 467	196	**1.29**	1.12–1.49	109	**1.23**	1.02–1.48

Bold type indicates that the 95% CI does not include 1.00.
Abbreviations: O, observed; Pyrs, person-years.

Discussion

To our knowledge, this is the first systematic study in patients with AId on the risks and survival in histological types of brain tumors. The data showed increased risks mainly for meningioma, for which the SIR was increased overall, and after 7 individual AIds. The SIR was also increased for neurinoma in patients with systemic sclerosis and for hemangioma/hemangioblastoma in patients with multiple sclerosis. These increases can most likely be ascribed to surveillance bias when relatively benign tumors were serendipitously diagnosed during hospitalization for AId. For the most aggressive tumor, glioma, no increased risks were observed. However, of note, no decreased risks were found either. Thus, the reported data on the protective effects of allergic conditions against brain tumors, discussed in the Introduction, appear not to hold for the present 33 AI conditions.[7,8] We studied risks of many cancers after AIds. The only mechanistic clue from these studies has been that cancer risk may be increased at the organ that is targeted by AId; for example, small intestinal and colon adenocarcinomas were increased in patients with Crohn disease and ulcerative colitis.[12]

The data on survival showed overall decreases for glioma and meningioma. Survival for both of these tumors was decreased among patients with chronic rheumatic heart disease, multiple sclerosis, and rheumatoid arthritis. The highest HR (5.41) for all gliomas was found among patients with immune thrombocytopenic purpura (HR was 13.56 for high-grade glioma). For meningioma, the highest HRs were observed among patients with amyotrophic lateral sclerosis (7.66) and systemic lupus (6.41). If surveillance bias influenced diagnostics of meningioma, as suggested above, it may bias survival toward a favorable direction, because nonsymptomatic early cases were likely to survive better than the symptomatic cases. In the present study, data were presented for all tumor types on overall survival, although cause-specific survival was also analyzed. For glioma, all increased HRs for overall survival were also replicated for glioma-specific survival. In the separate analysis of survival in low- and high-grade gliomas, the overall HRs did not differ. However, after several individual AIds, significant increases in HRs were observed for high-grade glioma, which was also more common than low-grade glioma. For meningioma and neurinoma, both with good survival, hardly any cause-specific deaths were recorded, and only overall HRs were reported. Overall survival is also preferred, because for persons with an underlying AId and subsequently cancer, the death registrar may have difficulties in deciding what the underlying cause of death was.

What would be the reasons for the observed impaired survival associated with glioma and meningioma in some AIds? Any comorbidity may potentially interfere with the overall survival through the mortality burden of that other disease or its weakening of the patient's physical condition. Comorbidity may also limit therapeutic options.[15–17] The decreased survival in amyotrophic lateral sclerosis, multiple sclerosis, and chronic rheumatic heart disease could indicate the inherent mortality associated with these conditions. Immune thrombocytopenic purpura, associated with poor survival in glioma, would probably limit surgical interventions, which are standard treatments for glioma.

The apparently improved survival from the early (1964–1990) to the late (1991–2008) period in chronic rheumatic heart disease, systemic lupus, and ulcerative colitis may be ascribed to the improved overall survival in these AI conditions. However, for chronic rheumatic heart disease and ulcerative colitis, glioma-specific survival also improved. Multiple sclerosis was the only AId with moderate case numbers for which the overall survival from brain cancer and glioma-specific survival appeared to decrease between the 2 periods. A partial explanation may be that the first period brain cancers in patients with multiple sclerosis were not diagnosed or reported to the Cancer Registry as efficiently as in the latter period, when imaging techniques were improved. Differential diagnostics, particularly, in the early period were probably not always successful, and reporting of a second life-threatening disease (glioma) was perhaps considered to be superfluous. Some support to this notion was the higher number of glioma cases (1.28-fold) and deaths (2.20-fold) after multiple sclerosis than after other AIds in the latter period, compared with the former period.

The strengths of the present study are its size, nationwide coverage, and high diagnostic accuracy of both AIds and brain tumors. The weaknesses include lacking data on treatment and other clinical details. It is important to indicate that at least the serious AIds are treated to a large extent in hospitals in Sweden, because the specialist health care is concentrated to hospitals and the costs are largely covered by the health care system.[18] Multiple comparisons are a recognized problem in studies involving numerous statistical testing. Because there are no previous studies with which we could compare the present findings, we have focused on results with reasonable case numbers and with replication in the present study among brain cancer subtypes.

In conclusion, the present data showed increased risks mainly for meningioma, most likely as a result of incidental finding. No increased or decreased risks were noted for glioma. The data on survival showed overall decreases for glioma and neurinoma, and the survival in both was decreased among patients with chronic rheumatic heart disease, multiple sclerosis, and rheumatoid arthritis. In total, HRs were increased for glioma after 6 AIds and for meningioma after 7 AIds.

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