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Myasthenia and risk of cancer: a population-based case–control study

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Background and purpose: To evaluate the association between having non-thymoma myasthenia and the risk of extra-thymic cancer in a population-based setting.

Methods: A nationwide case–control study was conducted in Denmark based on medical registries. The study included all cases with a first time diagnosis of cancer during 2000–2009. Each case was matched by birth year and gender with eight population controls using risk set sampling. Subjects with myasthenia were identified through a validated register-based algorithm. Conditional logistic regression was used to compute crude and adjusted odds ratios (ORs), with 95% confidence intervals (CIs), for cancer associated with a prior diagnosis of myasthenia.

Results: In all, 233 437 cases and 1 867 009 controls were identified. A total of 80 cases and 518 controls had a prior diagnosis of myasthenia. Myasthenia was not associated with an increased risk of overall cancer (OR 1.1; 95% CI 0.9–1.4). Adjusted ORs for major cancer sites were also close to unity, whereas an elevated risk of lymphomas was observed (OR 2.0; 95% CI 0.8–5.5). Early-onset myasthenia was associated with a slightly increased OR for overall cancer (1.5; 95% CI 1.0–2.3); however, this estimate was based on small numbers.

Conclusions: Non-thymoma myasthenia was not associated with an increased risk of overall cancer. Larger studies are necessary to evaluate the association between myasthenia and risk of lymphoma and the potential effect modification by age of myasthenia onset in relation to cancer risk.

Introduction

Acquired myasthenia gravis (myasthenia) is an autoimmune disorder causing muscle weakness and fatigability [1,2]. The disease is characterized by antibodies targeting components of the neuromuscular junction [2]. Onset of myasthenia can occur at any age; amongst younger individuals it is more frequent in women than in men, but after the age of 50 years slightly more men than women are diagnosed with the disease [3].

Approximately 10% of myasthenia patients harbour a thymoma, and these patients are at increased risk of extra-thymic cancer [4–6]. However, whether non-thymoma myasthenia *per se* is linked to an increased risk of extra-thymic cancer is also of interest, since it has been suggested that autoimmune disorders may be associated with an inherent risk of cancer due to inflammatory activity or genetic factors [7,8]. A potential association between non-thymoma myasthenia and cancer development is difficult to address due to the fact that treatment of myasthenia often includes long-term immunosuppression with drugs with established carcinogenic effects, such as azathioprine [9]. To address such methodological issues, studies of cancer risk amongst myasthenia patients should include detailed information on long-term drug use, ideally in a population-based setting. Only one population-based study has specifically examined the risk of extra-thymic cancer in patients with myasthenia

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[10]. That study was conducted in Taiwan and reported a 34% increased risk of cancer in patients with myasthenia compared with age-, gender-, and comorbidity-matched population controls without myasthenia.

Denmark has an array of nationwide registries that offer unique opportunities to identify patients and population controls, track their use of drugs over long periods of time, and ascertain subjects who develop cancer [11]. These nationwide register data were used to examine the association between having myasthenia and the risk of cancer.

Material and methods

Using the population-based Danish registries a case–control study of the association between myasthenia and risk of cancer was performed. The specific codes used to identify patients with myasthenia and classify their drug use and other characteristics are presented in the Appendix.

Setting

A data set retrieved from several registries comprising all incident cancer cases in the Danish population in 2000–2009 and age- and sex-matched controls from the background population was used [12].

Data from the following registries were linked: (i) the Danish Civil Registration System [13]; (ii) the Danish Patient Registry [14]; (iii) the Danish Prescription Registry [15]; (iv) the Danish Cancer Registry [16]; and (v) the Danish Pathology Registry [17]. Data were also used from an *ad hoc* registry, the Antibody Registry, created by merging test results on acetylcholine receptor antibody (AChR-ab) from two laboratories providing services for roughly half the Danish population since 1977 [18]. Our data sources have been described in more detail elsewhere [18,19].

Case ascertainment and selection of controls

Cases were persons with a primary diagnosis of histologically verified cancer (except non-melanoma skin cancer) in the Cancer Registry during 2000–2009. The date of the cancer diagnosis was used as the index date. Cases had to have resided in Denmark for at least 10 years prior to the index date and to have had no history of cancer (except non-melanoma skin cancer) or thymoma (irrespective of malignancy) (Appendix). Using risk set sampling [20] and applying the same selection criteria as for cases, each case was matched to eight controls by birth year, gender and calendar year. Within each risk set controls were assigned an index date corresponding to the date of diagnosis for the case. Cases were eligible as controls before they became cases. Thereby, the OR is an unbiased estimate of the incidence rate ratio (IRR) [20] that would have emerged in a cohort study in the same source population.

Identification of subjects with myasthenia

For all subjects, discharges (1977–2009) and outpatient visits (1995–2009) with a diagnosis code of myasthenia were identified in the Patient Registry. From the Prescription Registry, all information on dispensed prescriptions of pyridostigmine during 1995–2009 was retrieved. In the Antibody Registry, patients with a recorded positive AChR-ab test were identified and the first date of a positive test was noted.

Using a validated method [18], subjects were classified as suffering from myasthenia when they fulfilled at least two of three criteria: (i) a primary diagnosis code of myasthenia in the Patient Registry, (ii) at least two pyridostigmine prescriptions in the Prescription Registry or (iii) a positive AChR-ab test.

Myasthenia onset was defined as the earliest date of the following events: date of diagnosis code, first pyridostigmine prescription or date of positive AChR-ab test. The age at onset of myasthenia and the duration of myasthenia were calculated based on this date.

Exposure assessment and analyses

From the Prescription Registry, all prescriptions redeemed by cases and controls from 1995 to the index date, including information on statins, azathioprine, 'other immunosuppressants' (methotrexate, ciclosporine, tacrolimus, cyclophosphamide, mycophenolate mofetil), low-dose aspirin and non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) were retrieved.

Conditional logistic regression was used to compute crude and adjusted ORs (and 95% CI) for cancer associated with myasthenia. The results were stratified according to myasthenia duration (<5, ≥5 to <10, ≥10 years) and age of myasthenia onset (<50, ≥50 to <70, ≥70 years).

In the regression model, factors with a possible association with cancer risk were included: use of the selected drugs and history of rheumatoid arthritis, inflammatory bowel disease or diabetes. Furthermore, history of chronic obstructive pulmonary disease (COPD) as a proxy measure for heavy tobacco smoking was included. Exposure to drugs prior to the index date was defined as a cumulated dose of at least 500 defined daily doses within 5 years. The Charlson

Comorbidity Index (CCI) score [21] was also included, categorized into CCI scores of 0, 1 and 2+.

To further evaluate the potential confounding influence from tobacco smoking, risk estimates for the composite end-point of the following tobacco-related cancer types were examined: cancers of buccal cavity and pharynx, oesophagus, stomach, colorectum, liver, pancreas, nasal cavity and paranasal sinuses, larynx, lung, cervix, ovary, kidney, renal pelvis or ureter, urinary bladder or myeloid leukaemia [22]. The results were also stratified according to gender. In addition, the analyses were repeated after exclusion of subjects who only fulfilled one criterion for myasthenia who were defined as not suffering from myasthenia in main analyses. Finally, the main analyses were stratified by cumulative dose of azathioprine and/or other immunosuppressants as proxy for severity of myasthenia. All analyses were performed using Stata release 12.1 (StataCorp, College Station, TX, USA).

The study was approved by the Danish Data Protection Agency and Statistics Denmark's scientific board.

Results

In all, 233 437 patients with incident cancer (cases) and 1 867 009 controls during the study period, 2000–2009, were identified (Table 1). In univariate analyses, inflammatory bowel disease, diabetes, rheumatoid arthritis and COPD were more prevalent amongst cases, although differences were generally small. Similarly, overall comorbidity as measured by CCI was higher amongst cases (≥2: 14.4%) than amongst controls (10.7%) (Table 1).

The overall prevalence of myasthenia was similar between cases and controls. Eighty-two cases (0.034%) and 518 (0.028%) controls had a diagnosis of myasthenia (Table 1). Median time [interquartile range (IQR)] from diagnosis of myasthenia until index date was 8.5 years (IQR 3.8–15.6) amongst cases and 8.7 years (IQR 3.6–15.8) amongst controls. Amongst cases, 49% of the myasthenia patients were women. The corresponding figure was 43% amongst controls. A more pronounced gender difference was seen amongst patients with early-onset (<50 years) myasthenia, amongst whom women comprised 85% in the case group and 68% in the control group.

The adjusted OR for overall cancer associated with a prior diagnosis of myasthenia was 1.1 (95% CI 0.9–1.4) (Table 2). Similarly, adjusted ORs for the selected major cancer sites were close to unity, whereas the OR for lymphomas was elevated (OR 2.0; 95% CI 0.8–5.5). In analyses stratified by gender, age at index date or duration of myasthenia, no apparent association was found between myasthenia and overall cancer risk (Tables 3 and 4). Patients with early-onset myasthenia experienced an increased risk of overall cancer (OR 1.5; 95% CI 1.0–2.3) (Table 4), but with no consistency in risk estimates for women (OR 1.8; 95% CI 1.1–2.9) and men (OR 0.7; 95% CI 0.3–2.1). The sub-analyses and sensitivity analyses yielded results similar to those of the main analyses (data not shown).

Table 1 Characteristics of cases with cancer and population controls, Denmark, 2000–2009. Numbers (percentages) unless otherwise stated

	Cases (N = 233 437)	Controls (N = 1 867 009)
Men	113 932 (48.8)	911 147 (48.8)
Women	119 505 (51.2)	955 862 (51.2)
Age, years		
<50	30 216 (12.9)	241 762 (12.9)
50–70	109 665 (47.0)	877 247 (47.0)
70+	93 556 (40.1)	748 000 (40.1)
History of		
Myasthenia	80 (0.034)	518 (0.028)
Inflammatory bowel disease	2178 (0.9)	14 532 (0.8)
Diabetes	19 219 (8.2)	128 321 (6.9)
Rheumatoid arthritis	1704 (0.7)	12 002 (0.6)
COPD	15 629 (6.7)	77 869 (4.2)
Charlson Comorbidity Index score		
0	152 194 (65.2)	1 336 596 (71.6)
1	47 558 (20.4)	329 956 (17.7)
2+	33 685 (14.4)	200 457 (10.7)
Use of drugs[a]		
Azathioprine	282 (0.1)	1342 (0.1)
Prednisolone/prednisone	4691 (2.0)	30 536 (1.6)
Other immunosuppressants[b]	1252 (0.5)	8734 (0.5)
Aspirin	38 038 (16.3)	293 608 (15.7)
Non-aspirin NSAIDs	12 649 (5.4)	95 349 (5.1)
Statins	20 644 (8.8)	162 509 (8.7)

[a]Defined by use of at least 500 defined daily doses over the past 5 years; [b]methotrexate, ciclosporine, tacrolimus, cyclophosphamide, mycophenolate mofetil.

Discussion

In our nationwide study, non-thymoma myasthenia was not associated with an increased risk of overall cancer. An excess of lymphoma in patients with myasthenia and a slightly increased risk of overall cancer amongst women with early-onset myasthenia was observed, but the statistical precision of these analyses was limited.

Whilst several studies have examined the risk of cancer within populations of myasthenia patients [4,5,23,24], only few studies have compared the cancer risk of subjects with myasthenia with that of suitable controls without myasthenia [6,10,25]. In a study of

Table 2 Myasthenia and risk of cancer in Denmark

Cancer site	Cases, myasthenia, yes/no	Controls, myasthenia, yes/no	Odds ratio (95% confidence interval)	
			Crude	Adjusted[a]
All malignancies	80/233 357	518/1 866 491	1.2 (1.0–1.6)	1.1 (0.9–1.4)
Tobacco-related cancers	39/113 346	259/906 625	1.2 (0.9–1.7)	1.0 (0.7–1.5)
All non-tobacco-related cancers	41/120 011	259/959 866	1.3 (0.9–1.8)	1.2 (0.8–1.6)
Colon	10/20 806	50/166 441	1.6 (0.8–3.2)	1.4 (0.7–2.8)
Lung, bronchus and pleura	11/29 547	59/236 383	1.5 (0.8–2.9)	1.3 (0.7–2.5)
Breast	10/38 207	75/305 622	1.1 (0.6–2.1)	1.1 (0.6–2.1)
Prostate	11/22 912	79/183 259	1.1 (0.6–2.1)	1.1 (0.6–2.1)
Lymphoma[b]	5/8301	18/66 418	2.2 (0.7–6.0)	2.0 (0.8–5.5)
Other	33/113 584	237/908 368	1.1 (0.8–1.6)	1.0 (0.7–1.4)

[a]Adjusted for Charlton Comorbidity Index score, history of diabetes, inflammatory bowel disease, rheumatoid arthritis, COPD, and use of low-dose aspirin, non-aspirin NSAIDs, statins, azathioprine and other immunosuppressants; [b]Hodgkin's and non-Hodgkin's lymphoma.

Table 3 The association between myasthenia and risk of cancer stratified by age and gender

	Cases, MG/no MG	Controls, MG/no MG	Odds ratio (95% confidence interval)	
			Crude	Adjusted[a]
Age, years				
<50	9/30 207	46/241 716	1.6 (0.8–3.2)	1.4 (0.7–2.9)
≥50 and <70	25/109 640	174/877 073	1.2 (0.8–1.8)	1.0 (0.7–1.5)
≥70	46/93 510	298/747 702	1.2 (0.9–1.7)	1.2 (0.9–1.6)
Gender				
Men	41/113 891	297/910 850	1.1 (0.8–1.5)	1.0 (0.7–1.4)
Women	39/119 466	221/955 641	1.4 (1.0–2.0)	1.2 (0.9–1.7)

[a]Adjusted for Charlton Comorbidity Index score, history of diabetes, inflammatory bowel disease, rheumatoid arthritis, COPD, and use of low-dose aspirin, non-aspirin NSAIDs, statins, azathioprine and other immunosuppressants.

Table 4 Risk of cancer according to myasthenia duration and age of onset

	Cases	Controls	Odds ratio (95% confidence interval)	
			Crude	Adjusted[a]
No myasthenia	233 357	1 866 491	1 (Reference)	1 (Reference)
Duration of myasthenia, years				
<5	25	166	1.2 (0.8–1.8)	1.1 (0.7–1.7)
≥5 and <10	20	123	1.3 (0.8–2.1)	1.1 (0.7–1.8)
≥10	35	229	1.2 (0.9–1.7)	1.1 (0.8–1.6)
Age of myasthenia onset				
<50	27	131	1.7 (1.1–2.5)	1.5 (1.0–2.3)
≥50 and <70	23	221	0.8 (0.5–1.3)	0.8 (0.5–1.2)
≥70	30	166	1.4 (1.0–2.1)	1.3 (0.9–1.9)

[a]Adjusted for Charlton Comorbidity Index score, history of diabetes, inflammatory bowel disease, rheumatoid arthritis, COPD, and use of low-dose aspirin, non-aspirin NSAIDs, statins, azathioprine and other immunosuppressants.

305 myasthenia patients from Japan, nine extra-thymic tumours (2.9%) were identified, which according to the authors was comparable to the occurrence in the background population; however, actual results for this comparison were not presented in the paper [25]. In a study based on data from the Norwegian Cause of Death Registry, 249 deceased patients with myasthenia were matched to a control group of sex- and age-matched subjects who had died in the same period [6]. In that study, myasthenia patients had a lower occurrence of malignant disease as underlying or contributing cause of death than the controls (8.8% vs. 27.2%, $P < 0.001$). However, as also pointed out by Liu *et al.* [10], the Norwegian study was prone to several methodological shortcomings [10]. To our knowledge, the only true population-based study of myasthenia and cancer risk published hitherto is the large register-based study by Liu *et al.* [10]. Liu *et al.* identified 2614 myasthenia patients and 15 684 myasthenia-free subjects from the background population in Taiwan who were followed up for incident extra-thymic cancer for an average period of 8 years. Totals of 122 myasthenia patients and 539 controls developed cancer, yielding an IRR for cancer associated with myasthenia of 1.4 (95% CI 1.1–1.7). Exclusion of patients with thymoma had little impact on the risk estimated (IRR 1.3). Slightly increased risk estimates were observed for lymphoma

(IRR 1.7; 95% CI 0.4–5.5), lung cancer (IRR 1.6; 95% CI 0.8–3.0) and breast cancer (IRR 1.6; 95% CI 0.9–2.8). Our largely null results are somewhat in contrast with those of the Taiwan study, with exception of the risk increase for lymphoma. The exact procedure for identifying cases of thymoma was not reported in the Taiwan study, and residual misclassification of thymoma status could partially explain the reported higher rates of cancer.

The discrepancy between the findings in Liu *et al.*'s study and our study could also stem from genetic and environmental exposure differences in the two populations. An incidence study of myasthenia in Taiwan [26], also using the Taiwanese NHI Database, reported an incidence pattern that differs from studies of mainly Caucasian populations [3,27]. Thus, the effect modification by age of myasthenia onset was not seen in the Taiwanese population, which could indicate fundamental differences between the two populations.

In sub-analyses it was found that patients with myasthenia were at increased risk of lymphoma. Notwithstanding the limited statistical precision, the increased risk of lymphoma observed in our and Liu *et al.*'s [10] studies is compatible with the fact that a large proportion of myasthenia patients are treated with azathioprine, an established carcinogenic agent for development of non-Hodgkin's lymphoma [9]. Although use of azathioprine or other immunosuppressants after 1994 was adjusted for, whether long-term exposure to immunosuppressants could explain the elevated risk estimates of lymphoma and cancer overall in women with early-onset myasthenia is possible, since the latter patients will tend to be exposed to particularly lengthy immunosuppressive therapy. Besides the left truncation of use of immunosuppressants, some treatment with immunosuppressants, e.g. rituximab, is hospital-based, further introducing exposure misclassification in our pharmacy-based study. In a previous study, a two-fold increased risk of lymphoma associated with a high cumulated dose and long-term use of azathioprine was found [19]. However, caution should be exercised in the interpretation of the above results which were all based on small numbers.

Our study has a number of strengths. The study was population-based and performed in a setting with free access to health services. Nationwide registries with continuously updated and accurate data on medical conditions, prescriptions, cancer diagnoses, vital status and migration on all Danish residents were used. Our approach thus eliminated recall bias and minimized selection bias. In a validation study of the algorithm for identification of myasthenia patients, the register diagnosis of myasthenia had a positive predictive value of 97% and a false positive rate of only 3% [18]. Therefore, the myasthenia register diagnosis is regarded as highly valid. Finally, cancer diagnoses were restricted to histologically verified cases, further enhancing case validity.

A number of potential weaknesses should also be considered. First, as noted above, drug use before 1995 was not available for study, which may have led to some misclassification of long-term exposure. However, by including cancer diagnosis from 2000 onward a minimum of 5 years' drug exposure history was ensured thereby reducing this potential bias. Secondly, obtaining data on thymus status is challenging in register-based studies. Virtually complete coverage for all types of thymoma was achieved by combining data from the cancer, patient and pathology registries. Some degree of misclassification for thymoma cases diagnosed prior to 1997 where identification in our study was based on cancer and patient registry data only cannot be ruled out, particularly because the cancer registry data on thymoma are incomplete for benign thymoma [28], but we believe that the magnitude of this misclassification is small. Thirdly, no information was available on disease severity, which according to Baecklund *et al.* [8] may influence the risk of cancer in patients with rheumatoid arthritis. Because of the observational design of our study, the possibility that severity and other inadequately measured confounders influenced our results cannot be excluded.

In conclusion, non-thymoma myasthenia was found not to be associated with an increased risk of overall cancer in Denmark. Larger studies are necessary to evaluate the risk of type-specific cancer, including lymphoma, and potential effect modification in subgroups defined by age, severity of myasthenia or comorbidity.

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Disclosure of conflicts of interest

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Appendix

List of codes used in the analysis

Hospital discharges codes	
Myasthenia	ICD-8: 73309 ICD-10: DG700
Chronic obstructive pulmonary disease	ICD-8: 490.00, 491.00, 491.01, 491.03 ICD-10: J42, J43, J44
Diabetes	ICD-8: 249.00, 249.09, 250.00, 250.09 ICD-10: E10-E14
Rheumatoid arthritis	ICD-8: 71219, 71239 ICD-10: M050, M051, M060
Inflammatory bowel disease	ICD-8: 56301, 56319, 56904, ICD-10: K50, K510, K511, K512, K513
Thymoma[a]	ICD-8: 226.19, 194.29 ICD-10: DD38.4, DC37.9
Anatomical Therapeutic Classification (ATC) codes	
Pyridostigmine	N07AA02
Aspirin	B01AC06, N02BA01, N02BA51
Anti-diabetics	A10
Azathioprine	L04AX01
Statins	C10AA
NSAIDs	M01A (M01AX not included)
Other immunosuppressants	L04AX03, L04AD01, L04AD02, L01AA01, L04AA06, L01XC02
Pathology Registry codes (SNOMED)	
Thymoma[a]	M85800, M85801, M85803, M85804, M85806, M85807, M85811, M85821, M85831, M85841, M85851

[a]Used to identify patients with thymoma prior to the index date who were subsequently excluded from the sample.