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Registration of Increased Risk of Brain Cancer after the Diagnosis of Multiple Sclerosis

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Abstract

Background: We studied the cancer comorbidity of 18,212 Danish Multiple Sclerosis (MS) patients.

Methods: Using data from the Danish National Patient Registry we identified all persons with a first-time MS diagnosis during 1980-2013. Cancer outcomes of the study cohort were ascertained using diagnoses from the Danish Cancer Registry. Patients with cancer prior to MS were excluded. We computed standardized incidence ratios with 95% confidence intervals calculated as the number of observed cancers relative to the expected based on national incidence rates by sex, age and calendar year.

Results: All sites of cancers in the CNS were significantly increased, namely cancers of 1) membrane of the brain and spinal meninges, 2) brain, as well as 3) spinal cord, cranial nerves and central nervous system. MS is a disease of the CNS, and the 3 CNS cancer groups were individually significant. Several other cancers were also increased, namely 1) overall cancer, 2) urinary bladder cancer, 3) metastases and non-specified cancer in lymph nodes and 4) basal cell carcinoma.

Conclusion: Multiple sclerosis is associated with increased registration of a range of cancers, in particular in the period following debut of MS. The results may be due to detection bias and misregistration. Finally, the results could be due to confounding.

Keywords: Multiple sclerosis; Cancer; Epidemiology

Introduction

Genetic epidemiological studies have shown that multiple sclerosis (MS) is associated with endogenous retroviral loci [1-7]. The endogenous retroviruses associated with MS are potential causative agents in relation to cancer as retroviruses can cause immunological neoplasms [8,9] and also more rarely solid tumors [10]. Recently, it was proposed that MS may be caused by an infective agent entering the brain through the vagus nerve [11]. Such infective agents may later induce cancer. Therefore, we hypothesized that various forms of cancer, especially those of the brain, could be more common in MS patients.

Methods

Using data from the Danish National Patient Registry we identified all hospital inpatients and outpatients with a first-time multiple sclerosis diagnosis between 1 January 1980 and 30 November 2013. Cancer outcomes of the study cohort were ascertained using diagnoses from the Danish Cancer Registry, which in general has high validity, with up to 95% to 98% completeness and accuracy of recorded diagnoses [12]. We excluded patients with a cancer diagnosis at any time before the MS diagnosis. Standardized incidence ratios (SIRs) with 95% confidence intervals were calculated as the number of observed cancers relative to the expected based on national incidence rates by sex, age and calendar year. The study included 18,212 first-time MS patients. We included all major forms of cancer in the study.

To examine if any temporal trend was present, we stratified the SIR for CNS cancer in our cohort by calendar year (1980-1994, 1995-2004 and 2005-2013).

Results

The main results are presented in Table 1. We found that risks of all sites of cancers in the CNS were significantly increased. This was true for cancers of 1) membrane of the brain and spinal meninx, 2) brain, as well as 3) spinal cord, cranial nerves and central nervous system. MS is a disease of the CNS, and the risks of all 3 cancer groups were individually increased. Moreover, we found indications that MS and cancers were co-observed in time. The incidence rates of the 3 cancers were increased approximately 20-fold in a 6 months period after the initial diagnosis of MS relative to the general population (Table 2) and the initial incidence rates were 10-fold higher than the average incidence rates in MS patients after the initial year.

Apart from the CNS cancers, we observed elevated SIRs for 1) overall cancer, 2) urinary bladder, 3) metastases and non-specified cancer in lymph nodes, 4) basal cell carcinoma, and 5) a non-significant increase in breast cancer. Similar findings have been reported by others [13], although not by all. We did not find any overrepresentation of the standard categories of leukemia and lymphoma among MS patients. There was no discernible calendar-year trend in the CNS cancers (data not shown).

Discussion

Natalizumab was only introduced in 2006 and is not likely to have induced the cancers.

A previous Danish report [14] did not find an increased incidence of CNS cancers among MS patients. Because our MS patients were hospital-treated there could be a tendency that these were the more serious cases. However, the sheer number of cases studied precludes a serious selection.

Cancer Group	Observed	Incidence Rate (per 1000 PYR[1]) (95% CI)	Expected	SIR (O/E[2]) (95% CI)
All	1535	9.02 (8.57-9.47)	1441.93	1.06 (1.01-1.12)
Oral Cavity	6	0.04 (0.01-0.07)	7.66	0.78 (0.29-1.71)
Esophagus	8	0.05 (0.02-0.08)	12.57	0.64 (0.27-1.25)
Stomach	11	0.07 (0.03-0.11)	16.36	0.67 (0.34-1.20)
Small intestine	6	0.04 (0.01-0.07)	2.99	2.01 (0.74-4.38)
Large intestine incl. Colon rectosigmoid	77	0.45 (0.36-0.56)	77.92	0.99 (0.78-1.24)
Rectum	32	0.19 (0.13-0.26)	42.57	0.75 (0.51-1.06)
Anal canal	7	0.04 (0.02-0.08)	4.73	1.48 (0.59-3.05)
Liver	6	0.04 (0.01-0.07)	9.25	0.65 (0.24-1.41)
Pancreas	31	0.18 (0.12-0.25)	26.89	1.15 (0.78-1.64)
Larynx	5	0.03 (0.01-0.06)	8.75	0.57 (0.19-1.33)
Lung, bronchi and trachea	151	0.89 (0.75-1.03)	135.85	1.11 (0.94-1.30)
Malignant melanoma	71	0.42 (0.33-0.52)	56.89	1.25 (0.97-1.57)
Other skin cancer (excl. Basal cell carcinoma)	32	0.19 (0.13-0.26)	38.88	0.82 (0.56-1.16)
Breast	255	1.50 (1.32-1.69)	238.56	1.07 (0.94-1.21)
External female genitalia	5	0.03 (0.01-0.06)	3.54	1.41 (0.46-3.29)
Cervix of uterus	25	0.15 (0.10-0.21)	22.19	1.13 (0.73-1.66)
Uterus	27	0.16 (0.10-0.22)	34.36	0.79 (0.52-1.14)
Ovary	32	0.19 (0.13-0.26)	28.25	1.13 (0.77-1.60)
Prostate	64	0.38 (0.29-0.47)	80.86	0.79 (0.61-1.01)
Testicle	5	0.03 (0.01-0.06)	6.86	0.73 (0.24-1.70)
Kidney	18	0.11 (0.06-0.16)	20.01	0.90 (0.53-1.42)
Urinary bladder	65	0.38 (0.29-0.48)	47.65	1.36 (1.05-1.74)
Membrane of the brain and spinal meninx	26	0.15 (0.10-0.22)	14.36	1.81 (1.18-2.65)
Brain	53	0.31 (0.23-0.40)	26.8	1.98 (1.48-2.59)
Spinal cord, cranial nerves and central nervous system	23	0.14 (0.09-0.20)	7.9	2.91 (1.84-4.37)
Thyroid gland	6	0.04 (0.01-0.07)	8.86	0.68 (0.25-1.48)
Hodgkin malignant lymphoma	2	0.01 (0.00-0.03)	3.95	0.51 (0.06-1.83)
Non-Hodgkin malignant lymphoma	40	0.24 (0.17-0.31)	42.53	0.94 (0.67-1.28)
Lymphoid leukaemia	10	0.06 (0.03-0.10)	12.78	0.78 (0.37-1.44)
Myeloid leukaemia	11	0.07 (0.03-0.11)	9.04	1.22 (0.61-2.18)
Metastases and non-specified cancer in lymph nodes	33	0.19 (0.13-0.27)	20.17	1.64 (1.13-2.30)
Other cancers with poorly specified localization and non-specified cancer	12	0.07 (0.04-0.12)	8.44	1.42 (0.73-2.48)
Basal cell carcinoma	346	2.03 (1.82-2.25)	308.71	1.12 (1.01-1.25)

[1] Person Years
[2] Observed/Expected

Table 1: Risk of specific cancer in multiple sclerosis patients, 1980-2013 only cancers with more than 4 cases among the MS patients were listed.

Membrane of the brain and spinal meninx	Observed	Person-years at risk	Incidence Rate (per 1000 PYR[1]) (95% CI)	Expected	SIR (95% CI)
0-6 Months	11	8832.9	1.25 (0.62-2.08)	0.5044	21.81 (10.87-39.02)
>6-12 Months	0	8485.3	–	0.4975	–
>12 Months	15	152931.5	0.10 (0.05-0.15)	13.3588	1.12 (0.63-1.85)
Brain					
0-6 Months	18	8832.9	2.04 (1.21-3.08)	1.1267	15.98 (9.46-25.25)
>6-12 Months	3	8485.3	0.35 (0.07-0.85)	1.0974	2.73 (0.56-7.98)
>12 Months	32	152931.5	0.21 (0.14-0.29)	24.5738	1.30 (0.89-1.84)
Spinal cord, cranial nerves and central nervous system					
0-6 Months	7	8832.9	0.79 (0.32-1.48)	0.31079	22.52 (9.03-46.40)
>6-12 Months	2	8485.3	0.24 (0.03-0.66)	0.30526	6.55 (0.79-23.65)
>12 Months	14	152931.5	0.09 (0.05-0.15)	7.2849	1.92 (1.05-3.22)

[1] Person Years

Table 2: CNS cancer in the period after diagnosis of multiple sclerosis.

The number of MS observed corresponds roughly to what is expected for Denmark [14]. We have no explanation for the discrepancy.

It is not clear if the CNS observations relate to surveillance bias or are genuine, biological phenomena. Several possible explanations may underlie the observed association. First, the observed increased cancer incidence in CNS could be due to detection bias: MR scans of the CNS during diagnostic work-up of MS could lead to detection of latent cancers. MR scanning was introduced in Denmark in 1984 at few centers but became widespread in the beginning of the 1990s and thus it was in full use in the two latest calendar-year strata of this investigation.

Detection bias is likely the primary factor driving the results but we are worried that 0.2% of the MS patients are diagnosed with the cancers within the initial 6 months period. Cancers of the meninges often remain latent for long periods of time but the increased incidence extend to the other cancer forms, too. If the 20-fold increased risk during the first 6 months of follow-up period was caused by detection bias, this would imply that all CNS cancers regularly can exist in a latent state for numerous years before it is accidentally detected by an MR scan. Also, SIRs for CNS cancer remained elevated more than 6 months after the initial diagnosis of MS. This is not consistent with a pile-up of hidden cancers revealed during diagnostic work-up of MS including MR scans as a mandatory element.

Secondly, the phenomenon could be due to misregistration. If a fraction of all CNS cancers in the population initially were misdiagnosed and registered as MS despite the widespread use of MR-scanning and the misdiagnosis remained in the registry when the correct diagnosis of cancer was later confirmed, this could partly drive the observed results.

Finally, a biological confounder may be at the root of the association. Of note, the most consistent findings across different investigations were the increases in bladder cancer risk, which hardly can be a result of MR surveillance bias or misregistration. It is it possible that some form of biological crisis elicits both MS and the cancers. One possibility would be a burst of retroviral replication.

Conclusion

In conclusion, we found that MS was associated with increased registration of numerous cancers. These findings warrant further investigation.

Conflicts of Interest

None.

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