Cancer risk in multiple sclerosis: findings from British Columbia, Canada

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Findings regarding cancer risk in people with multiple sclerosis have been inconsistent and few studies have explored the possibility of diagnostic neglect. The influence of a relapsing-onset versus primary progressive course on cancer risk is unknown. We examined cancer risk and tumour size at diagnosis in a cohort of patients with multiple sclerosis compared to the general population and we explored the influence of disease course. Clinical data of patients with multiple sclerosis residing in British Columbia, Canada who visited a British Columbia multiple sclerosis clinic from 1980 to 2004 were linked to provincial cancer registry, vital statistics and health registration data. Patients were followed for incident cancers between onset of multiple sclerosis, and the earlier of emigration, death or study end (31 December 2007). Cancer incidence was compared with that in the age-, sex- and calendar year-matched population of British Columbia. Tumour size at diagnosis of breast, prostate, colorectal and lung cancers were compared with population controls, matched for cancer site, sex, age and calendar year at cancer diagnosis, using the stratified Wilcoxon test. There were 6820 patients included, with 110 666 person-years of follow-up. The standardized incidence ratio for all cancers was 0.86 (95% confidence interval: 0.78–0.94). Colorectal cancer risk was also significantly reduced (standardized incidence ratio: 0.56; 95% confidence interval: 0.37–0.81). Risk reductions were similar by sex and for relapsing-onset and primary progressive multiple sclerosis. Tumour size was larger than expected in the cohort (P = 0.04). Overall cancer risk was lower in patients with multiple sclerosis than in the age-, sex- and calendar year matched general population. The larger tumour sizes at cancer diagnosis suggested diagnostic neglect; this could have major implications for the health, well-being and longevity of people with multiple sclerosis.

Keywords: multiple sclerosis; cancer; Canada; epidemiology; diagnostic neglect

Abbreviations: SIR = standardized incidence ratio

Introduction

Multiple sclerosis is a chronic neurological disease affecting ~1.3 million people worldwide (World Health Organization and Multiple Sclerosis International Federation, 2009). Although the underlying cause of multiple sclerosis is unknown and the aetiology is not well understood, it is thought to be an autoimmune
disease mediated by the degradation of myelin and destruction of axons in the CNS.

The immune system (in particular regulatory T cells) is likely to play a central role in both cancer and multiple sclerosis (Cools et al., 2007; Zozulya and Wiendl, 2008), therefore it is biologically feasible that multiple sclerosis is associated with an altered cancer risk.

Previous studies of cancer risk in multiple sclerosis have shown inconsistent findings; overall cancer rates have been reported as higher (Moller et al., 1991), lower (Bahmanyar et al., 2009; Lebrun et al., 2011) or no different (Midgard et al., 1996; Sumelahti et al., 2004) to the general population. Sex-specific reductions in risk have also been found in males (Nielsen et al., 2006) or females (Achiron et al., 2005) only. The influence of disease course (relapsing-onset or primary progressive) on cancer risk has not previously been examined, despite the suggestion of immunological differences between primary progressive and relapsing-onset multiple sclerosis (Hohlfeld, 2004) and considerable variation in the prevalence of primary progressive disease between cohorts (Tremlett et al., 2010). Ultimately, a better understanding of cancer risk in multiple sclerosis gained from epidemiological studies, combined with findings from the basic sciences, could provide clues to the underlying aetiology of this complex disease.

The objective of this study was to compare the incidence of all cancers and of specific types of cancer following onset of multiple sclerosis in a large Canadian multiple sclerosis cohort. The risk of cancer by sex and disease course was also assessed. The potential role of diagnostic neglect was investigated by comparing the local extent of cancer at diagnosis in the cohort with that in general population controls.

Subjects and methods

This was a retrospective cohort study using linkage of prospectively collected data from population-based clinical and administrative databases.

The British Columbia multiple sclerosis database contains demographic and clinical information on patients visiting the four multiple sclerosis clinics in the province of British Columbia since the first clinic opened in 1980 (Tremlett et al., 2010). Clinical information including date of disease onset, disease course and dates of exposure to all disease-modifying drugs or immunosuppressants has been systematically documented. All patients with definite or probable multiple sclerosis (Poser criteria) who were registered in the database, with a first clinic visit between 1 January 1980 and 31 December 2004 were selected and linked to the British Columbia Cancer Registry (hereafter referred to as ‘Cancer Registry’) files, the British Columbia Ministry of Health’s Registration and Premium Billing (hereafter referred to as ‘Health Registration’) Files and the British Columbia Vital Statistics death database. Data linkage was achieved by matching by unique personal health number, a life-long number assigned under the province’s mandatory universal health care plan.

The Cancer Registry contains information on all malignancies diagnosed in British Columbian residents since 1969; reporting is mandatory. Non-melanoma skin cancers have been systematically documented in specific years only (1970–1994 and 2003). For all incident malignant cancers, diagnosed between 1969 and 2007, the diagnosis date, type and site of malignancy and cancer staging data, were extracted for the multiple sclerosis cohort.

The Health Registration files include registration and cancellation dates for all residents enrolled in the provincial health care plan and were used to confirm residence in British Columbia. The health care system in British Columbia is mandatory and is a payer system (premiums are paid by the individual or the employer). The provincial health care registries have been used extensively for population-based research in British Columbia as well as other Canadian provinces and are considered to be a reliable source of the population denominator for health research studies (Roos and Nicol, 1999; Jutte et al., 2011). Deaths dates were accessed from the British Columbia Vital Statistics Agency, which captures >99% of deaths in the province.

The at-risk period for a malignant event began at the later of: onset of multiple sclerosis symptoms; residency in British Columbia or 1 January 1969 (the beginning of the Cancer Registry coverage); and ended at the earlier of: emigration from the province; death; or 31 December 2007 (the study end). In the rare event of unsuccessful linkage to the Health Registration files, patients were followed from their first multiple sclerosis clinic visit until the earlier of their most recent visit or study end. These unlinked patients were included in the main analysis and the potential influence of including them was assessed by sensitivity analysis (see below).

Standardized incidence ratios (SIRs) were calculated by the application of stratum-specific (sex, age and calendar year) cancer incidence rates from the general population of British Columbia (available from the Cancer Registry). The SIR is the ratio of the sum of the observed stratum-specific incidence rates divided by the sum of the expected stratum-specific incidence rates. SIRs were generated for all cancers combined (excluding non-melanoma skin cancers) and by individual cancer site, for all patients with multiple sclerosis, as well as by sex and disease course. SIRs for non-melanoma skin cancer during the years that data were available were also calculated. The analyses were further stratified by follow-up time (<2; 2 to <10 and ≥10 years). Corresponding 95% confidence intervals (CI) were calculated by the exact Poisson method.

To assess the sensitivity of our SIR estimates, we performed additional calculations limiting the cohort or the follow-up period to address potential biases. First, linkage to the Health Registration files was unsuccessful for ~4% of the cohort, mostly due to missing personal health numbers, and a further 5% of patients had more than one period of residency in British Columbia (i.e. health coverage was cancelled and then restarted). To assess the potential impact of including the unlinked cases and the discontinuous periods of health coverage, as performed in the main analysis, we included only linked patients with one continuous time period of provincial medical coverage. Secondly, to assess the risk of cancer in the treatment naive cohort, the follow-up period was truncated at the start of any disease-modifying drug or immunosuppressant (including clinical trial medications). Thirdly, to address potential survivor bias due to follow-up during the time period prior to the opening of the British Columbia multiple sclerosis clinics, we limited the start of our observation period to the later of 1 January 1986 or the onset of multiple sclerosis or residency in the province. Finally, the potential influence of considering probable multiple sclerosis cases was assessed by including only those with definite multiple sclerosis. All results of the sensitivity analyses were compared with those of the main analyses.

The primary tumour size (the ‘T’ component of the TNM staging classification (Sobin et al., 2009)) was compared between the multiple sclerosis and population control cancer cases for four of the most common types of cancer: breast, prostate (adenocarcinoma), colorectal...
and lung (non-small cell). Tumour size was categorized into four 
groups, T1 to T4; a higher number indicates a greater size or local 
extent of the primary tumour. The controls were matched to the mul-
tiple sclerosis cases by site of the malignant cancer, sex, age and cal-
endar year at cancer diagnosis and randomly selected from the Cancer 
Registry. To accommodate the matched data structure, tumour size 
was compared using the stratified Wilcoxon test (van Elteren test), 
where strata weights were inversely proportional to the stratum sizes.

Descriptive statistical analyses were carried out using the Statistical 
Package for the Social Sciences version 15 (SPSS Inc.); the calculation 
of SIRs and analyses that incorporated the stratified Wilcoxon test 
were conducted using R: A Language and Environment for Statistical 

Ethical approval was provided by the Research Ethics Boards of the 
University of British Columbia and the British Columbia Cancer 
Registry.

Results

A total of 6917 eligible cases were identified from the British 
Columbia multiple sclerosis cohort. Of these, 4998 (72%) were 
female and 1919 (28%) were male; the mean age at onset of 
multiple sclerosis was 31.2 (SD 9.6) years. The majority (6172; 
89%) had a relapsing course at onset, 694 (10%) had primary 
progressive disease and 51 (1%) had an unknown clinical course.

Linkage of the British Columbia multiple sclerosis data with the 
Health Registration files was successful for 6667 (96.4%) patients; 
a slightly higher proportion of relapsing-onset patients (97% 
relapsing-onset versus 93% primary progressive multiple sclerosis; 
P < 0.001) and females (96.7% females versus 95.6% males; 
P = 0.04) were successfully linked. While the age at onset of 
multiple sclerosis did not differ between linked and unlinked pa-
tients, those with earlier birth years (and who were generally first 
seen in the early clinic years) were less likely to be successfully 
linked. All patients were included in the analysis.

During 110,666 person-years of follow-up there were 410 inci-
dent malignant cancers (excluding non-melanoma skin cancers). In 
addition, 92 malignant non-melanoma skin cancers were detected 
during 47,969 person-years of follow-up. SIRs and 95% CIs for all 
cancers combined and by cancer site are shown in Fig. 1, and by 
sex and disease course in Table 1. Overall cancer incidence was 
lower than expected (SIR: 0.86; 95% CI: 0.78–0.94). This reduced 
risk was consistent across most cancer sites, but was statistically 
significant for colorectal cancer (SIR: 0.56; 95% CI: 0.37–0.81) 
and stomach cancer (SIR: 0.14; 95% CI: 0.01–0.75); although 
the latter cancer was rare, with only seven expected and one 
observed case. The SIR for all cancers remained significantly 
reduced after removal of colorectal cancers (SIR: 0.89; 95% CI: 
0.81–0.99). In contrast, the risk of some cancers was elevated, 
including: non-melanoma skin (SIR: 1.26; 95% CI: 1.02–1.55); 
brain (SIR: 1.81; 95% CI: 0.96–3.09) and bladder cancer (SIR: 
1.21; 95% CI: 0.73–1.88), although the 95% CIs included unity 
for the latter two cancers. The relative risk of brain cancer was 
highest during the first 2 years of follow-up (two incident cancers; 
SIR: 6.15; 95% CI: 0.75–22.2) and decreased as the follow-up 
duration increased.

The overall decreased risk of cancer and of colorectal cancer, 
was evident for females, males and for those with relapsing-onset 
or primary progressive multiple sclerosis (Table 1). The risk of 
non-melanoma skin cancer was significantly increased in 
relapsing-onset patients; although the risk in primary progressive 
patients was no different than expected.

Figure 1: SIRs and 95% CIs for all cancers combined and by specific cancer site for the multiple sclerosis cohort. Cancer sites with more 
than five events are represented. ‘All’ cancers excludes non-melanoma skin cancers. NH Lymphoma = non-Hodgkin’s lymphoma.
one-third of the lung and colorectal cancers had documented
Approximately two-thirds of breast and prostate cancers and
tumour size
Sensitivity analyses
Restriction of the cohort to only the patients that were successfully linked to the Health Registration files and to those with one continuous period of provincial health care coverage yielded 103,320 person-years of follow-up. The cancer risk (SIR: 0.89; 95% CI: 0.80–0.98) in this restricted cohort was similar to that derived from the main analysis. After censoring patients at their first observation period for cancer events was restricted to 1 January 1986 there were 94,608 person-years of follow-up, and the risks for overall cancer (SIR: 0.89; 95% CI: 0.80–0.98) and colorectal cancer (SIR: 0.60; 95% CI: 0.39–0.87) remained significantly lower than expected, although the magnitude of the effect was attenuated somewhat. The SIR among those with definite multiple sclerosis (person-years of follow-up: 103,228; SIR: 0.86; 95% CI: 0.76–0.94) was comparable to the SIR for the whole cohort.

Tumour size
Approximately two-thirds of breast and prostate cancers and one-third of the lung and colorectal cancers had documented tumour size data. Information was incomplete in situations where the primary tumour could not be assessed or where data was not provided to the registry. The proportion of available data was no different between the cases and the controls (P = 0.05 for all four cancer types). After removal of the cases and controls with unavailable tumour size data, 132 multiple sclerosis cancers (79 breast, 23 prostate, 20 lung and 10 colorectal cancers) and 34,554 general population cancers were included.

Discussion
We observed an overall reduced risk of cancer in our Canadian multiple sclerosis cohort in comparison with the general population. This was consistent for females and males, and for both relapsing-onset and primary progressive patients. The reduced cancer risk was particularly evident for colorectal cancer, although

Table 1 Standardized incidence ratios for cancer in the multiple sclerosis cohort, by sex and clinical course

<table>
<thead>
<tr>
<th></th>
<th>Females Person-years = 80,430</th>
<th>Males Person-years = 30,237</th>
<th>Relapsing-onset Person-years = 98,999</th>
<th>Primary progressive Person-years = 11,049</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events SIR (95% CI)</td>
<td>Events SIR (95% CI)</td>
<td>Events SIR (95% CI)</td>
<td>Events SIR (95% CI)</td>
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<tr>
<td>All cancersa</td>
<td>291 0.88 (0.78–0.99)</td>
<td>119 0.80 (0.67–0.96)</td>
<td>333 0.86 (0.77–0.96)</td>
<td>70 0.78 (0.61–0.99)</td>
</tr>
<tr>
<td>Bladder</td>
<td>9 1.36 (0.62–2.58)</td>
<td>10 1.10 (0.53–2.01)</td>
<td>15 1.29 (0.72–2.13)</td>
<td>4 0.99 (0.27–2.54)</td>
</tr>
<tr>
<td>Body of uterus</td>
<td>21 1.04 (0.65–1.59)</td>
<td>–</td>
<td>18 1.05 (0.62–1.66)</td>
<td>3 1.03 (0.21–3.02)</td>
</tr>
<tr>
<td>Brain</td>
<td>8 1.84 (0.79–3.62)</td>
<td>5 1.76 (0.57–4.11)</td>
<td>11 1.85 (0.93–3.31)</td>
<td>2 1.67 (0.20–6.01)</td>
</tr>
<tr>
<td>Breast</td>
<td>110 0.94 (0.77–1.13)</td>
<td>0</td>
<td>91 0.89 (0.72–1.09)</td>
<td>17 1.17 (0.68–1.87)</td>
</tr>
<tr>
<td>Cervix</td>
<td>8 0.84 (0.36–1.65)</td>
<td>–</td>
<td>8 0.92 (0.40–1.81)</td>
<td>0 –</td>
</tr>
<tr>
<td>Colorectal</td>
<td>18 0.57 (0.34–0.90)</td>
<td>10 0.54 (0.23–0.99)</td>
<td>24 0.62 (0.40–0.92)</td>
<td>4 0.34 (0.10–0.94)</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>1 0.63 (0.02–3.53)</td>
<td>1 0.46 (0.01–2.55)</td>
<td>1 0.36 (0.01–1.99)</td>
<td>0 –</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>1 0.64 (0.02–3.57)</td>
<td>0 –</td>
<td>1 0.49 (0.01–2.74)</td>
<td>0 –</td>
</tr>
<tr>
<td>Kidney</td>
<td>5 0.99 (0.32–2.31)</td>
<td>2 0.46 (0.06–1.66)</td>
<td>7 0.94 (0.38–1.95)</td>
<td>0 –</td>
</tr>
<tr>
<td>Larynx</td>
<td>1 1.27 (0.03–7.08)</td>
<td>0 –</td>
<td>1 0.49 (0.01–2.74)</td>
<td>0 –</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>6 1.00 (0.37–2.19)</td>
<td>4 0.99 (0.27–2.53)</td>
<td>8 1.00 (0.43–1.97)</td>
<td>2 1.02 (0.12–3.69)</td>
</tr>
<tr>
<td>Lung</td>
<td>35 0.92 (0.64–1.28)</td>
<td>21 0.97 (0.60–1.48)</td>
<td>39 0.85 (0.61–1.16)</td>
<td>15 1.11 (0.62–1.84)</td>
</tr>
<tr>
<td>Melanoma skin</td>
<td>12 0.83 (0.43–1.44)</td>
<td>3 0.49 (0.10–1.43)</td>
<td>12 0.67 (0.35–1.18)</td>
<td>3 1.11 (0.23–233)</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>4 1.51 (0.41–3.86)</td>
<td>1 0.56 (0.02–3.26)</td>
<td>4 1.20 (0.33–3.07)</td>
<td>1 1.01 (0.03–5.60)</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>9 0.77 (0.35–1.47)</td>
<td>4 0.56 (0.15–1.43)</td>
<td>10 0.66 (0.32–1.21)</td>
<td>3 0.88 (0.11–3.24)</td>
</tr>
<tr>
<td>Oral</td>
<td>2 0.36 (0.04–1.31)</td>
<td>5 0.89 (0.29–2.07)</td>
<td>4 0.45 (0.12–1.15)</td>
<td>2 0.90 (0.44–1.59)</td>
</tr>
<tr>
<td>Ovary</td>
<td>10 0.82 (0.39–1.51)</td>
<td>–</td>
<td>10 0.96 (0.46–1.76)</td>
<td>0 –</td>
</tr>
<tr>
<td>Pancreas</td>
<td>5 0.86 (0.28–2.01)</td>
<td>5 1.53 (0.50–3.58)</td>
<td>9 1.30 (0.59–2.47)</td>
<td>1 0.48 (0.01–2.69)</td>
</tr>
<tr>
<td>Prostate</td>
<td>35 0.91 (0.64–1.27)</td>
<td>35 0.91 (0.64–1.27)</td>
<td>23 0.90 (0.57–1.35)</td>
<td>11 0.89 (0.44–1.59)</td>
</tr>
<tr>
<td>Stomach</td>
<td>0 0.27 (0.01–1.51)</td>
<td>1 0.27 (0.01–1.51)</td>
<td>1 0.18 (0.01–1.00)</td>
<td>0 –</td>
</tr>
<tr>
<td>Testis</td>
<td>2 1.06 (0.13–3.82)</td>
<td>2 1.06 (0.13–3.82)</td>
<td>2 1.20 (0.15–3.42)</td>
<td>0 –</td>
</tr>
<tr>
<td>Thyroid</td>
<td>7 0.92 (0.37–1.89)</td>
<td>0 –</td>
<td>7 0.89 (0.36–1.83)</td>
<td>0 –</td>
</tr>
<tr>
<td>Non-melanoma skinb</td>
<td>59 1.28 (0.98–1.65)</td>
<td>33 1.23 (0.85–1.72)</td>
<td>76 1.35 (1.06–1.69)</td>
<td>16 0.96 (0.57–1.62)</td>
</tr>
</tbody>
</table>

a ‘All cancers’ excludes only non-melanoma skin cancers and includes rare cancers, such as gallbladder and trachea cancers, which were not assessed individually. Liver cancers were assessed individually: none were observed and no SIRs were generated for this cancer specifically.
b Person-years for non-melanoma skin cancer follow-up: total cohort = 47,969; relapsing-onset multiple sclerosis = 42,122; primary progressive multiple sclerosis = 56,35. Statistically significant SIRs (P < 0.05) are indicated by bold text.
this reduction alone did not explain the decreased overall risk. In contrast, an increased risk of non-melanoma skin cancer was observed.

To the best of our knowledge, this study is the first to investigate overall cancer risk in a North American multiple sclerosis cohort. Our findings were consistent with those from large European cohorts; that the overall risk of cancer was lower than expected for both females (Bahmanyar et al., 2009; Lebrun et al., 2011) and for males (Nielsen et al., 2006; Bahmanyar et al., 2009; Lebrun et al., 2011). Among the smaller studies of cancer risk in multiple sclerosis, one study of an Israeli cohort reported a decreased cancer risk for females but not for males (Achiron et al., 2005), while others were unable to detect a difference in risk (Midgard et al., 1996; Sumelahti et al., 2004). In contrast, authors reporting an increased risk of all combined cancers studied cohorts of multiple sclerosis patients identified via hospital discharge records (Moller et al., 1991; Goldacre et al., 2004), such findings may reflect cancer risk in patients with more severe multiple sclerosis or in patients with a greater propensity for comorbidities.

The elevated (non-significant) risk for brain cancer was most evident soon after disease onset, indicating that the diagnostic work-up of multiple sclerosis may provide an explanation (i.e., surveillance bias), as suggested by others who have observed an increased risk (Sumelahti et al., 2004; Bahmanyar et al., 2009; Fois et al., 2010). Other studies have reported no significant increase in brain cancer risk (Moller et al., 1991; Midgard et al., 1996; Nielsen et al., 2006; Lebrun et al., 2008).

We found an increased incidence of non-melanoma skin cancer that is consistent with others (Moller et al., 1991; Bahmanyar et al., 2009), although not with all previous studies. No difference (Nielsen et al., 2006) or a reduced risk (Goldacre et al., 2004) have also been reported. We observed this increased risk in relapsing-onset patients only, which could provide support for a possible link with corticosteroid use (Karagas et al., 2001; Sorensen et al., 2004; Jensen et al., 2009) because short courses would be used to treat relapses in this group. However, we were unable to verify or capture the use of corticosteroids. Alternative explanations might include surveillance bias as patients with multiple sclerosis interact more regularly with the health system; although this does not account for the lack of association in the smaller primary progressive group. The British Columbia Cancer Registry is one of the few registries worldwide capable of ascertaining non-melanoma skin cancer risk (Gallagher and Lee, 1998).

However, reporting of these cancers is often heterogeneous because they are frequently treated successfully without the need for specialist care or hospitalization, and only skin cancer cases with pathology confirmation are reliably reported. Challenges with capturing the occurrence of these cancers might explain differences in findings between studies. In contrast to the risk of non-melanoma skin cancer, melanoma incidence was lower than expected (although not significantly). While non-melanoma skin cancer has been associated with increased UV exposure and elevated levels of serum 25-hydroxyvitamin, vitamin D through diet or supplement use has been associated with a reduced risk of melanoma, although both associations have been inconsistent between studies (Gandini et al., 2009; Eide et al., 2011; Tang et al., 2011). Given the elusive and apparently complex relationship between skin cancer, UV exposure and vitamin D, our findings neither support nor refute the hypothesized protective role of UV or vitamin D in multiple sclerosis (Ascherio and Munger, 2007).

The reduced risk of digestive cancers (colorectal and stomach) in our cohort is consistent with findings from Scandinavia (Midgard et al., 1996) and a US veterans study (Landgren et al., 2011); further studies in France and England have reported a reduced risk (although not statistically significant) (Lebrun et al., 2008; Fois et al., 2010) and an older study found this risk to be no different to the general population (Moller et al., 1991). Lifestyle factors (particularly diet) have been associated with colorectal cancers, but dietary choices of people with multiple sclerosis have not been studied extensively. While it is feasible that a healthier diet is adopted following a diagnosis of multiple sclerosis (Leong et al., 2009), there is evidence to suggest that other cancer-related health behaviours, such as exercise, smoking and alcohol intake, are similar or even less ‘healthy’ in patients with multiple sclerosis compared with controls (Nortvedt et al., 2005; Pohar et al., 2007; Matrie et al., 2009). Because the overall cancer risk was reduced in our cohort, even when colorectal cancers were excluded, and because lower rates of cancer were observed across many of the less common cancer sites, it is likely that a more general mediator of reduced risk is responsible rather than a lifestyle influence specifically linked to one cancer type. Increased immunosurveillance (due to a more active immune system), a shared common genetic predisposition for multiple sclerosis and low cancer risk or delays in cancer diagnosis (diagnostic neglect) are all potential explanations.

We found evidence to suggest that diagnostic neglect might contribute to the apparent reduction in cancer risk in multiple sclerosis. There have been few investigations of this clinically important issue, although a Danish study reported larger breast
cancer tumours in a multiple sclerosis cohort compared with the general population (Nielsen et al., 2006). Our findings, together with those from Denmark (Nielsen et al., 2006) indicate that the potential for diagnostic neglect of cancer requires further attention by patients, physicians and researchers. Cancer detection may be compromised when a patient has a chronic disease such as multiple sclerosis due to some similarities in symptoms between the comorbidity and cancer, competing demands on the primary care physicians’ time or functional limitations that may influence patient access to cancer surveillance programmes. This diagnostic neglect can occur in other diseases, even when the underlying chronic disease necessitates regular contact with the medical system (Gonzalez et al., 2001; Terret et al., 2009). Studies of cancer screening behaviour in people with multiple sclerosis compared to the general population are lacking but there is evidence that females with physical disabilities, including those with multiple sclerosis, attend cervical screening tests less frequently than their peers without multiple sclerosis (Nosek and Howland, 1997) and more severe multiple sclerosis can be associated with less cancer screening participation (Cheng et al., 2001). Diagnostic neglect could have major implications for the health, well-being and longevity of people with multiple sclerosis; cancer is a leading cause of death worldwide and, among multiple sclerosis patients, accounts for between 20% and 30% of non-multiple sclerosis-related deaths (Sadovnick et al., 1991; Bronnum-Hansen et al., 2004; Grytten Torkildsen et al., 2008; Stenstad et al., 2009).

Our study includes a substantial population of patients with a clinical diagnosis of multiple sclerosis confirmed by neurologists specializing in multiple sclerosis, >27 years of prospective follow-up and population-based linked health data. Linkage of the British Columbia Multiple Sclerosis data to provincial Cancer Registry and provincial administrative data ensured reliable coding of cancer and death, and minimal loss-to-follow-up. We were unable to link <4% of the multiple sclerosis cohort to administrative health files. However, exclusion of these patients as well as those who left and then returned to the province did not impact findings. Our study provides an estimate of cancer risk in a cohort of both untreated and treated patients with multiple sclerosis. While it was not designed to address the impact of disease-modifying or immunosuppressant therapies on cancer risk, sensitivity analysis revealed that our estimates were no different for the treatment naïve cohort. As with any study of cancer risk that relies on diagnosis, identification or registration of patients sometime after onset of multiple sclerosis, there is the potential for survivor bias. If an individual developed cancer and died after onset, but before registration, this individual would not have been captured, potentially leading to an underestimate of cancer risk in the cohort. Our sensitivity analysis in which the cohort was compared to the general population only during the period after the clinics opened, was designed to address potential bias due to missed cancers in people with multiple sclerosis who did not survive long enough to register at the clinics. The resulting risk estimates revealed that a reduced risk of cancer was still evident and the magnitude of this bias appeared small, although not negligible. Potential survivor bias should be considered in all studies involving cohorts of patients that are susceptible to delays in diagnosis or cohort registration. Furthermore, it is important to acknowledge that we were unable to consider the role of potential confounders or modifiers of the relationship between multiple sclerosis and cancer risk such as family history of cancer, ethnicity, socioeconomic status, smoking, diet and exercise. Finally, interpretation of the risk estimates for individual cancer types should be approached with some caution because of the low number of cancer events in certain subgroups as well as the increased probability of chance findings when testing multiple hypotheses.

In summary, we report a significantly reduced risk of cancer overall, and colorectal cancer in particular, in a large North American cohort of patients with multiple sclerosis followed for an average of 16 years. This reduced risk was consistent in females and males, and in both relapsing-onset and primary progressive multiple sclerosis. Only non-melanoma skin cancer risk was increased and this was observed only in relapsing-onset patients. We found evidence suggesting a later stage at diagnosis for four of the major cancers, which may implicate diagnostic neglect as the explanation for the observed reduced cancer risk in multiple sclerosis.

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Supplementary material

Supplementary material is available at Brain online.
Cancer risk in multiple sclerosis

References


