Colorectal Cancer Survival in Multiple Sclerosis: A Matched Cohort Study

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Abstract
**Background and Objectives:** We tested the hypothesis that overall and cancer-specific survival following colorectal cancer diagnosis is lower in persons with multiple sclerosis (MS) than without MS, using a retrospective matched cohort design.

**Methods:** Using population-based administrative data in Manitoba and Ontario we identified persons with MS using a validated case definition, and linked these cohorts to cancer registries to identify those with colorectal cancer. We selected persons with colorectal cancer and without MS matching 4:1 on birth year, sex, cancer diagnosis year and region. We used Cox proportional hazards regression to compare all-cause survival between cohorts adjusting for age at cancer diagnosis, cancer diagnosis year, income, region, and Elixhauser comorbidity score. We compared cancer-specific survival between cohorts using a cause-specific hazards model. We pooled findings across provinces using random-effects meta-analysis. Complementary analyses using a subcohort from Ontario adjusted for cancer stage and disability status, as measured based on the use of home care or long-term care services.

**Results:** We included 338 MS cases and 1352 controls with colorectal cancer. The mean (SD) age at cancer diagnosis was 64.7 (11.1) years. After adjustment, MS was associated with an increased hazard for all-cause death which was highest six months post-diagnosis (hazard ratio [HR] 1.45; 95%CI: 1.19-1.76), then declined over time (HR [95%CI] 1 year: 1.34 [1.09-1.63], 2 years: 1.24 [0.99-1.56]; 5 years: 1.10 [0.80-1.50]). MS was associated with increased cancer-specific death at 6 months post-diagnosis only (HR 1.29; 95%CI: 1.04-1.61). After adjusting for cancer stage, MS was associated with an increased hazard of death due to any cause (1.60; 95%CI: 1.16, 2.21) and with cancer-specific death (HR 1.47; 95%CI: 1.02, 2.12). The association of MS and all cause death was partially attenuated after adjustment for disability status (HR 1.37; 95%CI: 0.97, 1.92), as was the association with cancer-specific death (HR 1.34; 95%CI: 0.91, 1.97).

**Discussion:** Overall and cancer-specific survival was lower in persons with than without MS in the early period following colorectal cancer diagnosis. Further study is warranted to determine what factors underlie these worse outcomes.
Introduction

People living with multiple sclerosis (MS) have a lower life expectancy than individuals without MS.\(^1\), \(^2\) Cancer has been reported as the second or third most common cause of death in adults with MS, following MS.\(^2\)-\(^4\) Based on a systematic review, the three most common incident cancers in the MS population are cervical, breast and colorectal cancers.\(^5\) Similarly, breast and colorectal cancers are two of the four cancers which account for half of cancer deaths in the adult general population.\(^6\) Recently, we found that women with MS had lower survival after breast cancer diagnosis than women without MS.\(^7\) This raises the question as to whether MS is associated with lower survival after other common cancers.

Relatively little is known about the association between MS and survival after colorectal cancer diagnosis.\(^8\) In a Swedish study, survival following cancers of the upper and lower gastrointestinal tracts was higher in an MS cohort than in a non-MS cohort;\(^8\) this surprising finding contrasts with those reported for persons with other serious chronic illnesses such as diabetes and psychiatric disorders.\(^9\), \(^10\) Accurate prognostic information about cancer is critical to support therapeutic decision-making by persons with MS and their care providers.

Using a population-based matched cohort study, we compared overall survival and cancer-specific survival after colorectal cancer diagnosis in persons with MS as compared to persons without MS. If survival were found to be lower in persons with MS this would indicate that further investigation of the cancer care trajectory such as participating in screening, time to diagnosis, and cancer treatment, and the role of MS-specific factors would be warranted.
Methods

Setting and Design

Forty-two percent of the Canadian population resides in the provinces of Manitoba and Ontario. We included these two provinces because of the combined population size of approximately 14 million people, as well as their differing sizes (Manitoba’s population is 1.4 million) and organization of health services, to improve generalizability of our findings. Each province is responsible for delivery of universal, publicly funded medically necessary services. As part of health systems management, these provinces prospectively record the use of health care services by nearly all residents in administrative databases. As privacy regulations do not permit person-level data to leave the province of origin, we applied the same protocol in each province.

In both provinces, the databases used included the respective provincial population registries; the Discharge Abstract Database (DAD); medical/physician services (in Ontario the Ontario Health Insurance Plan [OHIP]); and the Cancer Registry. In Manitoba, we accessed the administrative databases through the Manitoba Population Research Data Repository at the Manitoba Centre for Health Policy (MCHP). These databases were linked using an encrypted unique provincial identifier. In Ontario, we accessed administrative databases at ICES. ICES is an independent, non-profit research institute whose legal status under Ontario’s health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. These databases were linked using unique encoded identifiers and analyzed at ICES. The population registries provided sex, region of residence [postal code], dates of birth, dates of death, and dates of health care coverage. The DAD captures hospital admission and separation dates, and discharge diagnoses. These diagnoses are recorded using the International Classification of Diseases (ICD) system, either ICD-9-clinical modification (CM) or ICD-10-Canada (CA), depending on the year. Medical/physician services (OHIP) capture the date of service and physician-assigned diagnoses using 3-digit ICD-9 codes. In Ontario only, we accessed the Ontario Drug Benefit (ODB) database which captures prescription drug dispensions.
for all those aged ≥65 years and receiving home care or long-term care (i.e., nursing home). Use of the ODB allowed us to identify persons residing in long-term care settings. In Ontario we also accessed the Home Care Database which captures individuals who receive home care services since 2005. Since 1965, the Manitoba Cancer Registry has captured cancer cases in Manitoba since 1965, with a completeness of 95-98%.\textsuperscript{11} Cancer stage has been captured since 2004. Completeness of the Ontario Cancer Registry is 98%, and cancer cases have been recorded since 1964.\textsuperscript{12} Cancer stage data has been captured since 2007. We linked postal code to area-level Census data from Statistics Canada to determine the average household income of each individual's enumeration area.\textsuperscript{13}

\textit{Standard Protocols, Approvals and Consents}

The University of Manitoba Health Research Ethics Board and Queen’s Research Ethics Boards approved the study. The Manitoba Health Information Privacy Committee approved data access. Administrative data access (via ICES) was authorized under section 45 of Ontario’s Personal Health Information Protection Act.

\textit{Study populations}

The study period was January 1, 1994 to December 31, 2016. We applied a validated case definition which identified persons with MS as those who ever had ≥3 hospital or physician claims for MS based on ICD-9 or ICD-10-CA diagnostic codes (340/G35).\textsuperscript{14} For each person who met the MS case definition we sought the earliest ICD-9 or ICD-10 claim for central nervous system demyelinating disease to determine the MS diagnosis date. This prevalent MS cohort was linked to the Cancer registries. We then identified members of the MS cohort with incident colorectal cancer after MS diagnosis using ICD-O-3 topography codes (C18.0, C18.2-C18.9, C19.9, C20.9, C26.0). We designated the date of colorectal cancer diagnosis as the study index date. Next, we excluded anyone who: (i) did not have a valid provincial registration number; (ii) was not resident in the province with provincial health insurance for ≥12 months before the index date (eligibility is lost due to death or emigration); (iii) <18 years old at the index date; (iv) had any cancer before the index date; (v) had concurrent cancer, defined as subsequent cancer diagnosed within
six months after the index date; or (vi) had carcinoma in situ at diagnosis (Figure 1). This constituted the MS-colorectal cancer cohort. To identify a matched cohort, we selected all persons diagnosed with colorectal cancer without MS. We excluded anyone with diagnostic codes for any central nervous system demyelinating disease including MS, then applied the same exclusion criteria as for the MS cohort. From this pool of potential matches, we chose 4 persons matched on sex, year of birth ± 3 years, year of colorectal cancer diagnosis ± 2 years, and region of residence (first two digits of postal code) at the index date. Cases with fewer than 4 matches were excluded.

**Outcomes**

The primary outcome was overall survival (considering all causes of death, including MS) after colorectal cancer diagnosis, truncated at 5 years, reflecting that this is the typical benchmark in colorectal cancer. The secondary outcome was cancer-specific survival, defined as any cancer death and also truncated at 5 years. We also describe cancer stage at diagnosis to characterize the cohorts. The stage of cancers which originate from solid tumors is described using the Union for International Cancer Control (UICC) TNM classification of malignant tumors which considers the size of the primary tumor, whether it has invaded local tissue, regional lymph node involvement and presence of metastases; this information can be combined into an overall stage grouping which ranges from 0 (in situ) to IV, or unknown, for each cancer. Cancer stage was grouped as I/II and III/IV to allow consistent reporting across provinces while meeting privacy requirements not to report cell sizes smaller than 6.

**Covariates**

We included several covariates that are associated with cancer survival, including age at cancer diagnosis (continuous), region of residence (urban [reference group] vs. rural), socioeconomic status, cancer diagnosis year (1994-2004 [reference group], 2005-2009, 2010-2016) and comorbidity. In Ontario, we classified urban regions as communities with populations ≥100,000 based on the census metropolitan areas or census agglomeration. In Manitoba, we classified the only two cities (populations of 47,000 and 600,000) as urban. We categorized socioeconomic status, based on quintiles of average
household income, as lowest quintile, quintiles 2-4, and highest quintile [reference]). We included
cancer diagnosis year to account for temporal trends in colorectal cancer incidence and survival.\textsuperscript{17} We
used the Elixhauser comorbidity index (continuous variable) with a one year lookback period because it
adjusts better for comorbidity in cancer studies than other indices.\textsuperscript{18} The index was modified to exclude
cancer diagnosis codes so that we would not misclassify metastases or secondary cancers as
comorbidity. Similarly, we excluded paralysis and demyelinating disease codes to avoid misclassifying
MS-related symptoms as comorbidity. Notably, the index captures obesity and drug and alcohol abuse in
addition to chronic health conditions. We updated socioeconomic status, region (urban/rural), and
comorbidity status at the study midpoint to account for changes in status and address non-
proportionality identified during testing of Cox regression model assumptions. In Ontario, we also
measured disability status (as of 2007) based on receipt of home care services or admission to a long-
term care facility. Home care services are only provided to individuals with persistent impairments in
functional status. Nearly half of individuals with MS who receive home care in Canada use a wheelchair
and have some degree of cognitive impairment, one-third report suffer from falls, and one-third are
incontinent. When health care needs are too great to be met in the community, long-term care (i.e.
nursing home) is provided. In Canada, eight out of ten persons with MS residing in long-term care
require a wheelchair and have some degree of cognitive impairment, making long-term care admission a
highly specific marker of severe disability.\textsuperscript{19} We used $\geq 1$ OHIP fee code for services delivered in long-
term care, or the long-term care code in the ODB to identify long-term care admissions,\textsuperscript{20, 21} this
definition has a positive predictive value of 93.2\% and negative predictive value of 99.9\%.\textsuperscript{22} The earliest
long-term care code identified constituted the date of disability in that setting. Thus use of either home
care or long-term care indicated the presence of moderate to severe disability.

\textit{Analysis}

We characterized the cohorts using descriptive statistics including frequency (percent), mean (standard
deviation [SD]) and median (interquartile range [IQR]). The cohorts were compared using standardized
differences (values of 0.20-0.49 represent small effect sizes, 0.50-0.79 represent medium effect sizes, and values ≥0.80 represent large differences between cohorts in baseline characteristics). We reported crude case fatality rates (deaths per 100 person-years) in the two cohorts.

We used Cox proportional hazards models to examine the association between MS and all-cause survival following colorectal cancer diagnosis, where zero time was the colorectal cancer diagnosis date. Each participant was followed until emigration/loss of provincial health care eligibility, death due to any cause or the end of the study period (December 31, 2016), whichever came first. Since follow-up varied between the MS and matched cohorts due to differential survival, the matching factors were included as covariates, along with the other covariates described above. In colorectal cancer, comorbid diseases such as MS may influence the stage of illness at diagnosis, and cancer stage is associated with survival.

Also, a study in British Columbia, Canada found as compared to persons without MS, persons with MS had larger tumors at diagnosis with colorectal, breast, lung or prostate cancers. Therefore, we did not adjust for cancer stage in the primary model as we considered it a causal intermediate; that is, a mediator of the association between MS and survival (Figure 1). We tested the proportional hazard assumption using graphical methods and time-dependent covariates. This assumption was not met for the MS vs. non-MS variable; the violation of the assumption was more pronounced in Manitoba than in Ontario. Therefore, we included an interaction term between MS and the natural log of time, and we report hazard ratios at 6 months, 1 year, 2 years and 5 years post-diagnosis.

To test the association between MS and cancer-specific survival, we used a cause-specific hazard model which accounted for the competing risk of death to other (non-cancer) causes, and adjusted for the same covariates as for the all-cause survival model. In each regression model we tested for interactions between cohort (MS vs. controls) and age; and cancer diagnosis year. We used random-effects meta-analysis to pool adjusted hazard ratios (HR) and 95%CIs from the regression models. We reported $I^2$ as a measure of heterogeneity of the findings between provinces, where $I^2 \leq 25\%$ indicates low heterogeneity, and $I^2 \geq 75\%$ indicates high heterogeneity.
**Complementary analysis**

We conducted several complementary analyses. First, for our primary model, we calculated the E-value to determine the sensitivity of our findings to unmeasured confounders, where the E-value is a function of the strength of association (HR) of the exposure (i.e. MS) and the outcome (i.e. death). It describes the strength of association needed between an unmeasured confounder and both the exposure and the outcome to explain away the observed association of interest.\(^{31,32}\) Second, among individuals in Ontario diagnosed in ≥2007 for whom cancer stage data were available, we incorporated stage (in 4 separate groups) as a covariate, viewing stage as a potential mediator of the association between MS and survival (Figure 1). Notably, the proportional hazards assumption for the MS vs. non-MS variable was not violated for the subcohort, but there was an interaction between stage and age. This analysis was not possible in Manitoba due to the small size of the cohorts. Third, we explored the association between disability status and survival in Ontario, where the study population was large enough, to understand how much of potential survival differences were mediated by differences in underlying disability between those with MS and those without (Figure 1). We expected that including this covariate would attenuate the association between MS and survival.

Statistical analyses were performed using SAS V9.4 (SAS Institute Inc., Cary, NC).

**Data Availability**

The source data for MB are not owned by the researchers or MCHP and as such cannot be provided to a public repository. With the appropriate approvals, the MB data can be accessed through the MCHP. The ON dataset from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at [www.ices.on.ca/DAS](http://www.ices.on.ca/DAS).

**Results**

**Study Populations**
After we applied the inclusion and exclusion criteria, we identified 338 MS cases and 1352 non-MS controls with colorectal cancer (Figure 2). As expected, the MS and non-MS cohorts were similar with respect to the matching factors of sex, age (year of birth), year of cancer diagnosis, and region (Table 1). The peak age group at diagnosis of colorectal cancer was ≥70 years, followed by 60-69 years. Over forty percent of subjects were diagnosed in 2010 or later, and most lived in urban settings. In the MS and matched cohorts combined, subjects (reported from 2004 onward in Manitoba and 2007 onward in Ontario: 436/1246, 35.0%) were diagnosed with stage I or II colorectal cancer. This did not differ between cohorts (stage I/II cancer: MS 93/201 (46.2%), controls 343/810 (42.3%); stage III/IV cancer: MS 92/201 (45.8%), controls 417/810 (51.5%), p = 0.30).

Survival

The 5-year case fatality rate was 41% higher in the MS cohort than in the matched cohort (Figure 3, Table 2). As expected, cancer-specific case fatality rates were lower in both cohorts, but the cancer-specific fatality rate was 27% higher in the MS cohort than in the matched cohort (Figure 4, Table 2). Overall, of the 150 members of the MS cohort who died due to any cause, 115 (76.7%) were due to cancer, and 18 (12.0%) were secondary to MS as the underlying cause.

After adjustment for age at cancer diagnosis, cancer diagnosis year, income quintile, region, and Elixhauser comorbidity score, MS was associated with an increased hazard for death which was greatest at 6 months post-cancer diagnosis, then diminished such that it was no longer statistically significant by 2 years post-diagnosis (Table 3), in the context of a smaller population at risk. MS was also associated with an increased hazard of cancer-specific death, but only at 6 months post-diagnosis (Table 3). We did not observe any statistical interactions between cohort and either age at the index date or year of diagnosis.

In Ontario, cancer stage data were available from 2007 onward; this subcohort included 162 individuals with MS and 664 individuals without MS. Within this subcohort, 49 (30.2%) individuals with MS and 69 (10.4%) without MS were disabled. Individuals with MS were also less likely to have stage IV cancer at
diagnosis (13%) than individuals without MS (19.7%, standardized difference = 0.18). When we repeated the main analysis in the Ontario cohort on members diagnosed in 2007 or later, the associations between MS and death due to any cause (HR 1.22; 95%CI: 0.89, 1.68) and due to cancer-specific death (HR 1.09; 95%CI: 0.76, 1.56) were not statistically significant. After adjusting for cancer stage, MS was associated with an increased hazard of death due to any cause (1.60; 95%CI: 1.16, 2.21) and with cancer-specific death (HR 1.47; 95%CI: 1.02, 2.12). The association of MS and all cause death was partially attenuated after adjustment for disability status (HR 1.37; 95%CI: 0.97, 1.92), as was the association with cancer-specific death (HR 1.34; 95%CI: 0.91, 1.97).

Discussion

In this population-based retrospective study, we compared survival following colorectal cancer diagnosis in cohorts with and without MS. In our main analysis, we found that all-cause survival was lower in the MS cohort in the first 6-12 months following diagnosis, and cancer-specific survival was lower in the first 6 months following diagnosis. Based on $I^2$, there was no heterogeneity in the estimates between the two provinces. Our analyses testing the sensitivity of our findings to unmeasured confounders suggest that only factors associated with MS and survival with a strength of association exceeding 5.8 could account for our findings. In our analyses of the Ontario subcohort of members diagnosed in 2007 or later, MS was associated with lower all-cause and cancer-specific survival after accounting for cancer stage. Among those with MS who died, three-quarters of deaths were due to cancer and 1 in 8 deaths were due to MS as the underlying cause. This is a shift from the usual distribution in the MS population as a whole; in Manitoba 54.1% of deaths were attributed to MS during the period 2000 to 2011.²

To our knowledge, only one other study has examined survival following gastrointestinal cancer in persons with MS. Over the period 1969-2005, 280 persons with MS in Sweden had better survival following any gastrointestinal cancer than 4820 persons without MS, after adjusting for age, sex, region and socioeconomic status.⁸ Survival specifically following colorectal cancer diagnosis was not reported. Cancer-specific survival was also not reported. Consistent with our findings, other serious comorbid
chronic conditions are associated with lower survival after colorectal cancer diagnosis. In a 2018 systematic review of 35 studies, patients with colorectal cancer suffering from comorbid conditions had an increased risk of thirty day (HR 1.71; 1.26-2.31), overall (HR 1.41; 1.23-1.62), and cancer-specific death (HR 1.06; 1.02-1.10).\textsuperscript{10}

We considered cancer stage to be a potential mediator of survival based on the literature in MS and other comorbid diseases; that is, that MS might influence cancer stage at diagnosis. In the Ontario subcohort, people with MS were slightly less likely to have stage IV cancer at diagnosis, so that when we accounted for cancer stage, the association between MS and death was strengthened. The adverse effects of comorbidity on survival in colorectal cancer appear to differ according to cancer stage.\textsuperscript{25} For example, in a sample of 35,755 adults aged 67 years and older diagnosed with colorectal cancer, comorbidity was associated with reduced survival; the effect was greatest in early stage cancer.\textsuperscript{33} Efforts have been made to generate better estimates of survival according to age and sex by incorporating comorbidity scores,\textsuperscript{34} but MS was not included among the comorbidities considered.

In our primary analysis, survival was lower in the MS cohort particularly in the first six to twelve months. In our complementary analyses, we did not observe this time-dependent effect and survival in the MS cohort was lower throughout the entire five year post-cancer follow-up period. In Canada and other countries, population-based cancer registry data show that colorectal cancer survival generally has improved over time, particularly in the first year after diagnosis;\textsuperscript{15} however, improvements in survival have differed across groups. In Ontario between 1993 and 2009, colorectal cancer-specific survival improved more for people in the highest income quintile than in the lowest income quintile.\textsuperscript{35} The reasons for lower survival in the MS cohort are uncertain. These may include under-treatment of the cancer or reduced resilience to cope with the effects of cancer and treatment toxicity. Following diagnosis, the primary treatment of colorectal cancer involves surgery to remove the tumor. In individuals <75 years old, higher comorbidity burden is associated with a lower likelihood of receiving curative cancer resection.\textsuperscript{36, 37} Comorbidity is also associated with a lower likelihood of receiving
adjuvant chemotherapy at all ages. The surgery and the associated complications may be more difficult for persons with MS to tolerate than for persons without MS due to existing morbidity. In a prior Canadian study of 2104 persons with MS, those who were hospitalized accrued substantially increased MS-related disability following their hospitalizations. Individuals with MS are also more likely to die following serious health events such as acute myocardial infarctions and after intensive care unit admission; the risk of death is higher at 30 days after these events than at 365 days. Individuals with higher burdens of comorbid disease or polypharmacy may not be good candidates for adjuvant chemotherapy. Predictors of death from colorectal cancer within six months of diagnosis include metastatic disease (captured in cancer stage), age, and performance status. This is consistent with observations that frailty in older cancer patients is associated with increased post-operative mortality, post-operative complications, and intolerance to cancer treatment. In persons with MS, disability is strongly associated with frailty. Our disability measure aimed to capture individuals with poor performance status based on their use of home care and long-term care services; most individuals in such Canadian settings are frail. Although our exploratory analyses including disability as a covariate should be viewed cautiously due to the modest number of subjects affected and the focus on more severe forms of disability, they raise the possibility that disability mediates some of the association between MS and reduced survival in colorectal cancer. Future studies should capture a broader range of disability status and disability measures and examine whether they are associated with under-treatment or early adverse outcomes such as post-operative complications and mortality or intolerance to chemotherapy. A better understanding of colorectal cancer pathways, including diagnostic delays, adequacy of diagnostic processes and staging, treatment decisions, treatment intervals and intensity of treatment, multispecialty coordination of care, and adequacy of follow-up testing and detection of cancer recurrence, and outcomes could be helpful for clinicians counselling persons with MS as they attempt to balance the benefits of cancer treatment with the potential adverse effects and toxicity in the context of life expectancy, quality of life, and their existing health status. Another area that warrants
investigation is how accommodating the cancer care system is for people with disabilities, and how the system could be modified to better serve these individuals.

This study had several strengths including the population-based design executed in two provinces. We identified the MS cohort using a validated case definition, and identified colorectal cancers using high quality registries. Unlike the limited prior studies of cancer survival in MS, we assessed all-cause and cancer-specific survival. Our regression models accounted for temporal trends in cancer diagnosis, sociodemographic factors, and comorbidity. This study also had limitations. We used a comorbidity index that performs well in cancer studies; however, we may not have accounted for all relevant comorbidities.\(^{18}\) We used a broad definition of cancer death rather than death specifically due to colorectal cancer as physicians tend to report a non-specific site on death certificates rather than the specific (primary) site, potentially leading to underestimates of cancer-specific deaths.\(^{45-47}\) The administrative data we used lacked information regarding race, ethnicity, and health behaviors, factors that may influence colorectal cancer survival;\(^{48,49}\) however, we accounted for the most important prognostic factors including cancer stage and age.\(^{48,49}\) Other prognostic factors such as molecular features of the cancer were not captured, but there is no known reason these would differ between people with and without MS.\(^{50}\) Also, our E-value analysis suggested that any such factors would be unlikely to fully account for our findings given that the known effects of these factors are modest. We could not assess how exposure to disease-modifying therapy may influence cancer survival within the MS cohort because Ontario lacks population-based prescription data for persons <65 years and the number of cancer cases in Manitoba was relatively small. Future studies should investigate the mechanisms by which cancer survival is lower in persons with MS by considering the entire care cancer pathway.

We found that early survival was lower in persons with MS than without MS following the diagnosis of colorectal cancer. This has potential implications for clinical decision-making and further study is warranted to determine what factors underlie these worse outcomes.
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Table 1. Demographic characteristics of multiple sclerosis (MS) and matched colorectal cancer populations

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</tr>
<tr>
<td>2005-2009</td>
<td>74 (24.1)</td>
<td>311 (25.3)</td>
<td>7 (22.6)</td>
<td>25 (20.2)</td>
</tr>
<tr>
<td>≥2010</td>
<td>141 (45.9)</td>
<td>554 (45.1)</td>
<td>9 (29.0)</td>
<td>37 (29.8)</td>
</tr>
<tr>
<td>Income quintile at index, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quintile 1</td>
<td>58 (18.9)</td>
<td>235 (19.1)</td>
<td>6 (19.4)</td>
<td>23 (18.6)</td>
</tr>
<tr>
<td>Quintiles 2-4</td>
<td>190 (61.9)</td>
<td>745 (60.7)</td>
<td>14 (45.2)</td>
<td>78 (62.9)</td>
</tr>
<tr>
<td>Quintile 5</td>
<td>59 (19.2)</td>
<td>244 (19.9)</td>
<td>9 (29.0)</td>
<td>20 (16.1)</td>
</tr>
<tr>
<td>Urban region of residence at index, n (%)</td>
<td>261 (85.0)</td>
<td>1,047 (85.3)</td>
<td>21 (67.7)</td>
<td>79 (63.7)</td>
</tr>
<tr>
<td>Elixhauser score, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>173 (56.4)</td>
<td>719 (58.6)</td>
<td>18 (58.1)</td>
<td>76 (61.3)</td>
</tr>
<tr>
<td>&gt;1</td>
<td>134 (43.6)</td>
<td>509 (41.4)</td>
<td>13 (41.9)</td>
<td>48 (38.7)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.67 (1.95)</td>
<td>3.05 (1.89)</td>
<td>2.60 (2.11)</td>
<td>2.99 (1.96)</td>
</tr>
<tr>
<td>----------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
</tbody>
</table>

a- Missing for ≤5 controls in Ontario at index; s – cell sizes ≤5 suppressed to protect privacy; Std Diff = standardized difference
Table 2. Five-year all-cause and cancer-specific case fatality rates (95% confidence intervals) per 100 person-years in multiple sclerosis cases and matched controls

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Ontario</th>
<th>Manitoba</th>
<th>Pooled RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MS</td>
<td>Matched controls</td>
<td>MS</td>
</tr>
<tr>
<td>Person-years</td>
<td>818.6</td>
<td>3749.9</td>
<td>80.7</td>
</tr>
<tr>
<td>Overall</td>
<td>16.4</td>
<td>11.5</td>
<td>19.8</td>
</tr>
<tr>
<td></td>
<td>(13.8, 19.4)</td>
<td>(10.5, 12.6)</td>
<td>(12.2, 32.4)</td>
</tr>
<tr>
<td>Cancer-specific</td>
<td>12.7</td>
<td>9.9</td>
<td>13.6</td>
</tr>
<tr>
<td></td>
<td>(10.5, 15.4)</td>
<td>(8.9, 11.0)</td>
<td>(7.55, 24.6)</td>
</tr>
</tbody>
</table>

^a p = 0.0002, I^2 = 0% (p = 0.74); ^b p = 0.03, I^2 = 0% (p= 0.67)
Table 3. Adjusted\(^a\) hazard ratios (95% confidence intervals) for the association between multiple sclerosis and mortality following colorectal cancer

<table>
<thead>
<tr>
<th>Survival (MS vs. matched cohort)</th>
<th>Ontario</th>
<th>Manitoba</th>
<th>Pooled Estimate(^b)</th>
<th>(I^2)</th>
<th>E-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>1.45 (1.19, 1.76)</td>
<td>1.48 (0.41, 5.30)</td>
<td><strong>1.45 (1.19, 1.76)(^d)</strong></td>
<td>0</td>
<td>8.53 (3.31, 27.8)</td>
</tr>
<tr>
<td>1 years</td>
<td>1.33 (1.08, 1.63)</td>
<td>1.45 (0.68, 3.08)</td>
<td><strong>1.34 (1.09, 1.63)(^c)</strong></td>
<td>0</td>
<td>5.80 (2.12, 16.3)</td>
</tr>
<tr>
<td>2 years</td>
<td>1.21 (0.95, 1.55)</td>
<td>1.42 (0.78, 2.60)</td>
<td>1.24 (0.99, 1.56)</td>
<td>0</td>
<td>4.03 (1.00, 12.6)</td>
</tr>
<tr>
<td>5 years</td>
<td>1.08 (0.78, 1.49)</td>
<td>1.39 (0.42, 4.55)</td>
<td>1.10 (0.80, 1.50)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Cancer-specific(^c)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 months</td>
<td>1.30 (1.04, 1.62)</td>
<td>1.09 (0.28, 4.17)</td>
<td><strong>1.29 (1.04, 1.61)(^f)</strong></td>
<td>0</td>
<td>4.85 (1.59, 15.1)</td>
</tr>
<tr>
<td>1 years</td>
<td>1.11 (0.88, 1.42)</td>
<td>1.05 (0.49, 2.24)</td>
<td>1.11 (0.88, 1.40)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2 years</td>
<td>0.96 (0.72, 1.28)</td>
<td>1.01 (0.55, 1.83)</td>
<td>0.97 (0.75, 1.26)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5 years</td>
<td>0.78 (0.54, 1.15)</td>
<td>0.96 (0.27, 3.38)</td>
<td>0.80 (0.56, 1.15)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

\(a\)- Adjusted for age at index date, cancer diagnosis year, income quintile, region, Elixhauser comorbidity score; \(b\)- Pooled using random effects meta-analysis; \(c\)-Cause-specific hazard model; \(d\)- \(p = 0.0002\); \(e\)- \(p = 0.004\); \(f\)- \(p = 0.02\).
Figure 1. Directed acyclic graph of the association between multiple sclerosis and death after colorectal cancer diagnosis

![Directed acyclic graph](image1)

Figure 2. Flowchart of participant selection for analysis

![Flowchart](image2)
Figure 3. Kaplan Meier survival curves following colorectal cancer diagnosis in multiple sclerosis and matched cohorts*: (A) Ontario, (B) Manitoba

*s = suppressed to protect privacy and confidentiality

Figure 4. Cumulative incidence of death following colorectal cancer diagnosis in multiple sclerosis and matched cohorts: (A) Ontario, (B) Manitoba (non-cancer deaths suppressed due to small cell sizes)