RESEARCH ARTICLE

Multiple Sclerosis and the Cancer Diagnosis

Diagnostic Route, Cancer Stage, and the Diagnostic Interval in Breast and Colorectal Cancer

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Neurology® 2022;98:e1798-e1809. doi:10.1212/WNL.0000000000200163

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Abstract

Background and Objectives

The multiple sclerosis (MS) population's survival from breast cancer and colorectal cancer is compromised. Cancer screening and timely diagnoses affect cancer survival and have not been studied in the MS cancer population. We investigated whether the diagnostic route, cancer stage, or diagnostic interval differed in patients with cancer with and without MS.

Methods

We conducted a matched population-based cross-sectional study of breast cancers (2007–2015) and colorectal cancers (2009–2012) in patients with MS from Ontario, Canada, using administrative data. Exclusion criteria included second or concurrent primary cancers, no health care coverage, and, for the patients without MS, those with any demyelinating disease. We based 1:4 matching of MS to non-MS on birth year, sex (colorectal only), postal code, and cancer diagnosis year (breast only). Cancer outcomes were diagnostic route (screen-detected vs symptomatic), stage (stage I vs all others), and diagnostic interval (time from first presentation to diagnosis). Multivariable regression analyses controlled for age, sex (colorectal only), diagnosis year, income quintile, urban/rural residence, and comorbidity.

Results

We included 351 patients with MS and breast cancer, 1,404 matched patients with breast cancer without MS, 54 patients with MS and colorectal cancer, and 216 matched patients with colorectal cancer without MS. MS was associated with fewer screen-detected cancers in breast (odds ratio [OR] 0.68 [95% CI 0.52, 0.88]) and possibly colorectal (0.52 [0.21, 1.28]) cancer. MS was not associated with differences in breast cancer stage at diagnosis (stage I cancer, OR 0.81 [0.64, 1.04]). MS was associated with greater odds of stage I colorectal cancer (OR 2.11 [1.03, 4.30]). The median length of the diagnostic interval did not vary between people with and without MS in either the breast or colorectal cancer cohorts. Controlling for disability status attenuated some findings.

Discussion

Breast cancers were less likely to be detected through screening and colorectal cancer more likely to be detected at early stage in people with MS than without MS. MS-related disability may prevent people from getting mammograms and colonoscopies. Understanding the pathways to earlier detection in both cancers is critical to developing and planning interventions to ameliorate outcomes for people with MS and cancer.

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Glossary

CCI = Canadian Classification of Health Interventions; **CCP** = Canadian Classification of Procedures; **DAD** = Discharge Abstract Database; **HCD** = Home Care Database; **ICD** = International Classification of Diseases; **ICD-O** = International Classification of Diseases for Oncology; **MS** = multiple sclerosis; **NACRS** = National Ambulatory Care Reporting System; **OBSP** = Ontario Breast Screening Program; **OCR** = Ontario Cancer Registry; **ODB** = Ontario Drug Benefit; **OHIP** = Ontario Health Insurance Plan; **OR** = odds ratio; **PCCF** = Postal Code Conversion File; **RPDB** = Registered Persons Database; **SES** = socioeconomic status.

Survival after diagnosis of breast cancer or colorectal cancer is compromised for people with multiple sclerosis (MS).[1,2] Cancer screening, through early detection, and timely diagnosis are important drivers of cancer survival in breast and colorectal cancer.[3-7] Screen detection may be lower in persons with MS and a cancer diagnosis. The existing evidence in the MS population as a whole shows compromised access to cancer screening[8,9] and that women with MS who have mobility impairments are less likely to undergo preventative cancer screening than women with MS without mobility impairments.[10] Localized cancer stage is a measure of early detection and stage is strongly associated with cancer survival.[11] Diagnosis at an early stage, whether through screening or timely recognition of cancer symptoms, is an important aspect of cancer control. A protracted time from first presentation to diagnosis can affect survival when the cancer progresses during that time.[3,12] In patients with MS, longer diagnostic intervals might occur if cancer symptoms were mistakenly attributed to MS[13] or if cancer symptoms were less substantial than other competing health problems.[14]

We conducted a population-based study to assess the diagnostic process experienced by patients with MS and cancer. We documented 3 interconnected aspects of that experience: screening vs symptomatic detection, cancer stage (as an indicator of early detection), and how long it took for the diagnosis to be reached. We compared the experience of patients with MS to a set of matched patients without MS, looking separately at breast and colorectal cancer to examine whether findings were consistent across cancer types.

Methods

We conducted a population-based cross-sectional study in the province of Ontario, Canada, which is home to 39% of the Canadian population or 14.8 million people in 2020. Canada has universal health care with public funding of all medically necessary services.[15] Provincial governments are responsible for health care delivery and individually linked, routinely collected administrative health care data are available for research. We used data housed at ICES, an independent, nonprofit research institute. Data were linked using unique encrypted identifiers and analyzed at ICES Queen's.

Data Sources

We used previously created datasets.[1,2,16,17] Databases accessed included the Ontario Cancer Registry (OCR), the Discharge Abstract Database (DAD), the National Ambulatory Care Reporting System (NACRS), Ontario Health Insurance Plan (OHIP) medical and physician service claims, the Ontario Drug Benefit (ODB) database, the Ontario Breast Screening Program (OBSP), the Home Care Database (HCD), Census data along with the Postal Code Conversion File (PCCF), and the Registered Persons Database (RPDB). The OCR captures 98% of cancer cases in Ontario[18] using the International Classification of Diseases for Oncology (ICD-O-3); it contains cancer stage data collected from regional cancer registries and a centralized collaborative staging initiative.[19] The DAD provided hospital admission and discharge dates, diagnoses using ICD version 9 or 10, depending on the year, and procedures using the Canadian Classification of Procedures (CCP) to 2001 and the ICD-10–Canadian Classification of Health Interventions (CCI) thereafter. NACRS provided outpatient clinic visit data and emergency department data including dates, ICD-10 diagnoses, and CCP/CCI-coded procedures. OHIP claims recorded diagnoses using 3-digit ICD-9–based codes and procedure codes from the Ontario Schedule of Benefits. The ODB captures prescriptions for those in long-term care. The OBSP data provided information on mammographic screening. The HCD provided information about home care use. The Census combined with the PCCF provided information on area-level income and rurality. The RPDP provided demographic data. All data were linked at the individual person-level using an encrypted unique identifier or region of residence in the case of area-level variables.

Standard Protocol, Approvals, Registrations, and Patient Consents

This study was approved by the Queen's University Research Ethics Board. ICES' 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. Administrative data were accessed under section 45 of Ontario's Personal Health Information Protection Act.

Study Population

The study population consisted of all patients diagnosed with breast (C50.0–C50.9) or colorectal (C18.0, C18.2–18.9, C19.9, C20.9, C26.0) cancer who had a preceding diagnosis of MS and a set of matched patients without MS with breast or colorectal cancer. The study populations were drawn from cohorts developed for earlier work on this project.[1,2] Exclusions included non-Ontario residents, those <18 or >105

years of age at the cancer diagnosis, those who were diagnosed with cancer on the date of death, those whose breast or colorectal cancer was not their first cancer, those with a concurrent cancer diagnosis (diagnosed within 6 months), cancer stage = 0, men (breast cancer only), and those who were not OHIP eligible for ≥12 months before the cancer diagnosis. Also, for the patients without MS, we excluded those with any ICD-9/ICD-10-CA code for demyelinating disease (323, 377.3, 340, 341.9, G35, G36, G37) before their cancer diagnosis date.

Using data from April 1, 1994, through December 31, 2016, patients with MS were identified via a previously validated algorithm (99.5% positive predictive value, 96.1% negative predictive value) of ≥3 hospital or physician claims for MS using ICD-9 code 340 or ICD-10-CA diagnostic code G35.[20] The MS diagnosis date was assigned as the earliest occurrence of a hospital or physician claim for CNS demyelinating disease. Cancers in patients with MS were those occurring after the MS diagnosis.

Patients with cancer and without MS were 4:1 matched to those with MS on birth year (±2 years), sex (colorectal only), the first 2 digits of the postal forward sortation area, and diagnosis year (breast cancer only, 3-year groupings).

Data availability dictated the study years. Patients with breast cancer were diagnosed from 2007 through 2015 and patients with colorectal cancer were diagnosed from 2009 through 2012. Staging data are only available in Ontario at the population level since 2007.[19] Calculation of the diagnostic interval is a labor-intensive, complex process that we had undertaken in previous research covering these years.[16,17] We leveraged that work for this study. We included the smaller colorectal cancer population to expand the study's scope, recognizing that the statistical power in that group is low.

Outcomes

We studied 3 interrelated outcomes from the cancer diagnostic process: diagnostic route, cancer stage, and diagnostic interval. Whether a patient is diagnosed through a screening or a symptomatic route is associated with the cancer stage at diagnosis[7,21,22] and presenting symptoms are partly a function of cancer stage. Symptom severity can influence the urgency with which the problem is investigated, thereby influencing the length of the diagnostic interval[23] and, concurrently, longer diagnostic intervals have been associated with advanced stage cancer.[24] Symptomatic patients tend to wait longer than screened patients because they have the extra wait from first seeing a physician for symptoms to the first diagnostic investigation.[25] The median length of the interval is typically shorter in advanced stage cancer, likely due to more alarming presenting symptoms.[23,26] Staging investigations and the assignment of cancer stage happens around the end of the diagnostic process. Cancer stage distribution varies by diagnostic route: symptomatic patients are less likely to have early-stage cancer, screened patients more likely, and the proportion with stage IV is generally lower than stages II and III.[21,22] The availability of stage information in the registry most definitively represents the stage at the end of the diagnostic process rather than at the beginning. This aspect of the study design makes it cross-sectional because we are assuming that the stage group at diagnosis also represents the stage group at presentation.

Diagnostic route distinguished patients diagnosed via screening from those who presented symptomatically. For breast cancer, we identified screening mammograms on the first day of the patient's diagnostic interval using OBSP screening data and OHIP screening mammogram claims. All other patients with breast cancer were deemed symptomatic presentation. For colorectal cancer, the screened route was assigned to patients who had a fecal occult blood test, colonoscopy, lower gastrointestinal endoscopy, or polypectomy on the first day of their diagnostic interval. All others were deemed symptomatic presentation. For both cancer sites, cancer stage group I, II, III, or IV was assigned using the TNM Stage Classification System, 7th edition.[27] It is captured in the OCR as "best stage," meaning pathologic stage is used when available, otherwise clinical stage is used. The diagnostic interval was determined using a method we previously developed.[16] It involves the use of statistical control charts[28,29] to identify how far back in time before the cancer diagnosis we should collect cancer diagnosis–related encounters. All such encounters are collected for each patient and the earliest encounter defines index contact date or start of the diagnostic interval. The end of the interval is the diagnosis date in the OCR.

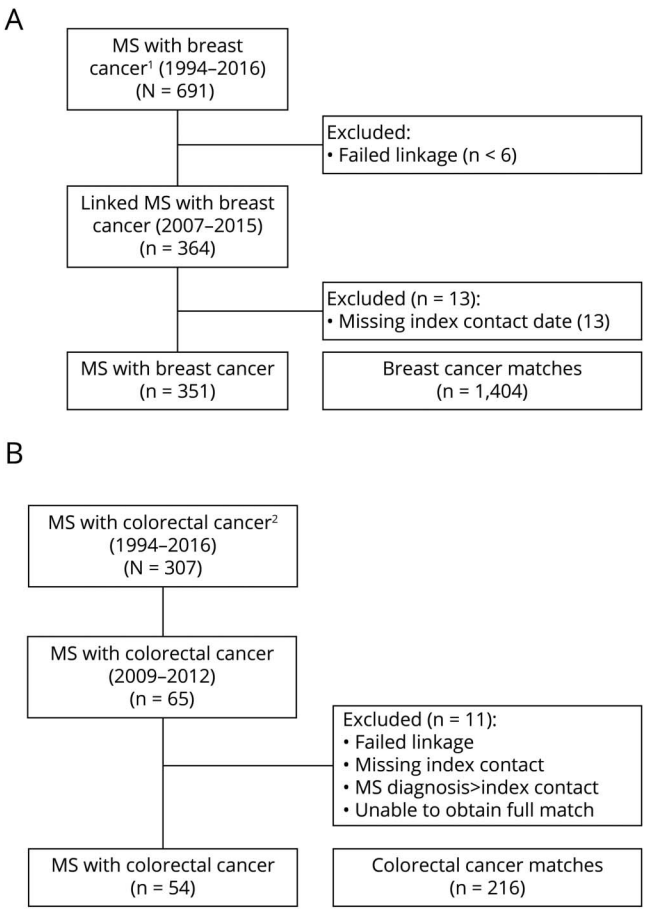
Covariates

Covariates included age at the diagnostic interval index contact date, sex (colorectal cancer only), socioeconomic status (SES), urban vs rural residence, comorbidity, and cancer diagnosis year. SES was represented by census dissemination area-level median household income, in quintiles. Urban residents were those living in communities of >100,000 based on census metropolitan or agglomeration area assignment. All other patients were classified as rural residents. Comorbidity was assigned using the Elixhauser comorbidity index[30] with a 2-year lookback before the diagnostic interval index contact date; cancer and potentially MS-related (demyelinating disease and hemiplegia) codes were excluded from the calculation. Moderate to severe disability status was captured based on use of home care services or long-term care residence in the year before the diagnostic interval index contact date. Home care services were available in the HCD. Long-term care residence was identified using records of OHIP services delivered in long-term care or ODB prescriptions in long-term care. In Ontario, home care services are provided to persons with persistently impaired functional status, and almost half of people with MS who receive home care in Canada use a wheelchair. Eighty percent of people with MS residing in long-term care require a wheelchair.[31]

Analysis

All analyses were conducted and reported separately for the breast and colorectal cancer cohorts. We compared the

Figure 1 Study Population Flowcharts



A) Breast cancer. (B) Colorectal cancer. MS = multiple sclerosis.

patients with and without MS by age, sex, SES, urban/rural residence, comorbidity, and diagnosis year using summary statistics (means and frequencies) and corresponding statistical tests (1-way analysis of variance and χ^2). We report diagnostic route and cancer stage frequencies and diagnostic interval medians, interquartile ranges, and 90th percentiles, and compare these between those with and without MS using the Kruskal-Wallis test. We also plotted the diagnostic interval distribution between those with and without MS.

Our multivariable analyses assessed whether patients with MS were less likely to have good outcomes (screen-detected presentation, stage I cancer, and a shorter diagnostic interval). We used multivariable logistic regression to examine the association between MS and our 2 categorical outcomes: diagnostic route (symptomatic as reference) and cancer stage (stage II, III, IV, and missing all grouped as the reference). In the case of cancer stage, we also conducted sensitivity analyses that excluded the missing stage group from the analyses. We controlled for age (continuous), sex (colorectal only), SES, urban/rural residence, and comorbidity index (0, 1, 2, 3+). The middle SES income quintiles 2 through 4 were combined into 1 category to increase study power. We used multivariable quantile regression to examine the association between MS and the length of the diagnostic interval. Quantile regression allows the evaluation of a relationship of an independent variable across the full range of a continuous dependent variable rather than its conditional mean and it does not require distributional assumptions. We evaluated the median and 90th percentile of the diagnostic interval, controlling for the same covariates, processed in the same way as our logistic regressions.

In addition to looking at each outcome separately, we conducted multivariable analyses to account for the interrelated nature of the outcomes. We assert that the diagnostic route was independent of both cancer stage and the diagnostic interval because it is the first step in the diagnostic process. Because the screened group was more likely to have early-stage cancer, we adjusted for diagnostic route to assess whether that changed the MS–stage association. The length of the diagnostic interval is affected by both diagnostic route and stage, so we adjusted for these variables separately and together to assess whether they changed the MS–diagnostic interval association. In conducting these analyses, our interest was in the persistence of the MS associations after adjustment for interrelated outcomes. Lastly, we assessed the role of disability on our MS associations when disability status was associated with both MS and our outcome in bivariate analyses.

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

Data Availability

The dataset from this study is held securely in coded form at ICES. Although legal data sharing agreements between ICES and data providers prohibit ICES from making the dataset publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at the ICES website. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Results

Breast Cancer

Fewer than 6 patients with MS and breast cancer were not linked and 13 were excluded due to missing diagnostic interval index contact dates (Figure 1). Overall, the breast cancer cohort included 351 patients with MS and 1,404 patients without MS. Matching variables showed high concordance between the MS and non-MS groups (Table 1). Mean age was 59 years. Overall, patients with MS were overrepresented in the higher SES quintiles ($p = 0.75$). Comorbidity burden was similar between the MS and non-MS groups. More patients with MS than without MS were disabled at the index contact date ($p < 0.0001$).

In unadjusted analyses, breast cancer in patients with MS was detected via screening 29.3% of the time, in contrast to 37.7% of

Table 1 Demographic Characteristics of the Multiple Sclerosis and Matched Cancer Populations

	Breast cancer			Colorectal cancer		
Variable value	**MS**	**Matched controls**	***p* Value**	**MS**	**Matched controls**	***p* Value**
N	351	1,404		54	216	
Age, y	58.8 (10.7)	58.8 (10.8)	0.98	62.3 (10.3)	62.2 (10.3)	0.93
Sex, F	351 (100.0)	1,404 (100.0)	NA	32 (59.3)	128 (59.3)	1.00
SES, income quintile[a]			0.75			0.09
1 (lowest)	50 (14.2)	226 (16.1)		16 (29.6)	45 (20.8)	
2	58 (16.5)	242 (17.2)		13 (24.1)	39 (18.1)	
3	71 (20.2)	297 (21.2)		11 (20.4)	30 (13.9)	
4	81 (23.1)	296 (21.1)		7 (13.0)	46 (21.3)	
5 (highest)	91 (25.9)	339 (24.1)		7 (13.0)	56 (25.9)	
Urban residence	307 (87.5)	1,247 (88.8)	0.48	43 (79.6)	182 (84.3)	0.41
Elixhauser score			0.59			0.19
0	105 (29.9)	471 (33.5)		11 (20.4)	68 (31.5)	
1	126 (35.9)	489 (34.8)		19 (35.2)	50 (23.1)	
2	68 (19.4)	259 (18.4)		16 (29.6)	58 (26.9)	
3+	52 (14.8)	185 (13.2)		8 (14.8)	40 (18.5)	
Disabled	74 (21.2)	66 (4.7)	<0.0001	18 (33.3)	15 (6.9)	<0.0001
Diagnosis year			0.64			0.72
2007	22 (6.3)	117 (8.3)		NA	NA	
2008	33 (9.4)	120 (8.5)		NA	NA	
2009	33 (9.4)	115 (8.2)		12 (22.2)	61 (28.2)	
2010	35 (10.0)	156 (11.1)		15 (27.8)	54 (25.0)	
2011	46 (13.1)	154 (11.0)		11 (20.4)	49 (22.7)	
2012	37 (10.5)	162 (11.5)		16 (29.6)	52 (24.1)	
2013	54 (15.4)	186 (13.2)		NA	NA	
2014	49 (14.0)	192 (13.7)		NA	NA	
2015	42 (12.0)	202 (14.4)		NA	NA	

Abbreviations: MS = multiple sclerosis; SES = socioeconomic status.
Values are mean (SD) or n (%).
[a] 4 breast cancer matched controls were missing SES.

the time in patients without MS ($p = 0.004$) (Table 2). There were small (non-statistically significant [$p = 0.32$]) differences in the breast cancer stage distribution; patients with MS were diagnosed with stage I cancer 38.2% of the time in contrast to 42.9% in patients without MS. The median breast cancer diagnostic interval in patients with MS was 35 days, similar to the median interval in patients without MS (34 days [$p = 0.85$]). Among those who waited the longest for their diagnosis (the 90th percentile), the diagnostic interval in patients with MS was 122 days, which was shorter than that observed in patients without MS (146 days). Figure 2A shows similar breast cancer diagnostic intervals in patients with and without MS.

Table 3 documents the relationships among our 3 outcomes in patients with breast cancer. All were statistically significant, with evidence of earlier stage and shorter diagnostic intervals among screen-detected patients compared to symptomatic patients, and shorter diagnostic intervals with more advanced stage cancer.

In adjusted analyses, the odds of breast cancer being detected through screening was 32% lower in patients with MS (Table 4). We further adjusted for disability status, given its association with MS (Table 1) and diagnostic route (breast cancer was screen-detected in 22.1% of patients with disability compared to 37.2% in those without disability [$p = 0.0004$]).

Table 2 Diagnostic Outcomes in the Multiple Sclerosis and Matched Cancer Populations

	Breast cancer			Colorectal cancer		
	MS	Matched controls	*p* Value	MS	Matched controls	*p* Value
N	351	1,404		54	216	
Diagnostic route						
Screened	103 (29.3)	529 (37.7)	0.004	7 (13.0)	45 (20.8)	0.19
Symptomatic	248 (70.7)	875 (62.3)		47 (87.0)	171 (79.2)	
Cancer stage						
I	134 (38.2)	603 (42.9)	0.32	16 (29.6)	41 (19.0)	>0.10
II	135 (38.5)	510 (36.3)		11 (20.4)	57 (26.4)	
III	52 (14.8)	190 (13.5)		17 (31.5)	58 (26.9)	
IV	13 (3.7)	57 (4.1)		s	34 (15.7)	
Unknown	17 (4.8)	44 (3.1)		s	26 (12.0)	
Diagnostic interval, d	35 (19–70)	34 (18–70)	0.85	96 (37–173)	72 (31–177)	0.47
90th percentile	122	146		292	331	

Abbreviation: MS = multiple sclerosis; s = cells sizes < 6 suppressed to protect privacy.
Values are n (%) or median (interquartile range).

The OR attenuated from 0.68 (95% CI 0.52, 0.88) to 0.79 (95% CI 0.61, 1.04). The adjusted odds ratio (OR) for early stage (stage I) cancer was lower in patients with MS, although this difference was not statistically significant (OR 0.81 [95% CI 0.64, 1.04]). This OR was somewhat attenuated when adjusted further for diagnostic route (OR 0.89 [95% CI 0.69, 1.15]). These results were similar in sensitivity analyses that excluded those with missing stage (OR 0.84 [95% CI 0.65, 1.07]) and with further adjustment for diagnostic route (OR 0.92 [95% CI 0.71, 1.19]). The median breast cancer diagnostic interval did not differ in individuals with and without MS after adjustment for covariates, diagnostic route, and stage. Among those who waited the longest for their diagnosis (the 90th percentile), the diagnostic interval was shorter for patients with MS, with a statistically significant difference of −18.5 days (95% CI −34.8, −2.2) after controlling for diagnostic route.

Colorectal Cancer

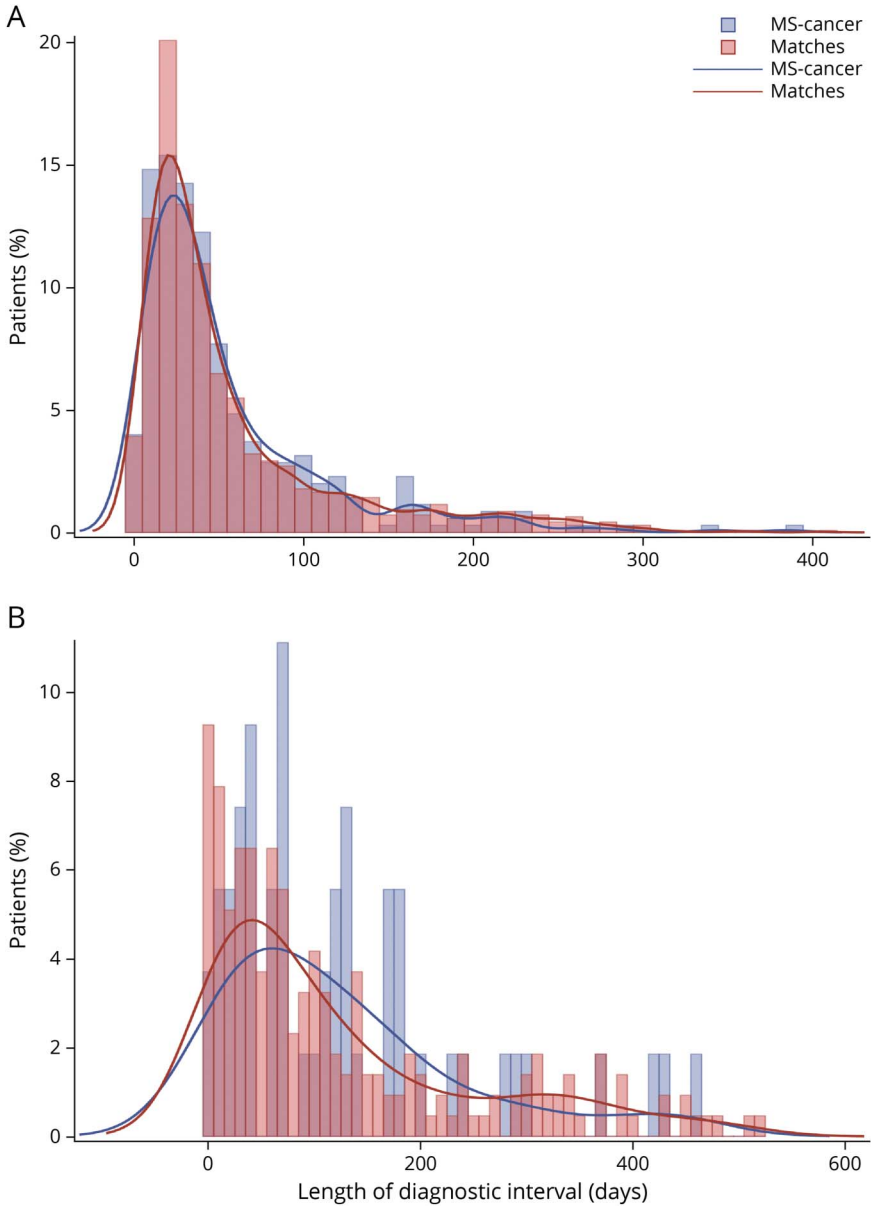
Eleven patients with MS and colorectal cancer were excluded due to failed linkage, missing index contact, because the MS diagnosis occurred after the cancer diagnosis, or because we could not achieve a 4:1 match (Figure 1). Our colorectal cancer cohort included 54 patients with MS and 216 patients without MS. The mean age was 62 years and 59% were female (Table 1). Patients with colorectal cancer and MS were more likely to be in the lower SES quintiles than those without MS, although this difference was marginal (p = 0.09). Among patients with colorectal cancer, those with MS appeared less likely to have no comorbid diseases than those without MS, although the difference was not statistically significant (p = 0.19). More patients with MS than without MS were disabled at the index contact date (p < 0.0001).

In unadjusted analyses, colorectal cancer in patients with MS was detected via screening 13.0% of the time. In contrast, 20.8% of colorectal cancer cases in patients without MS were detected via screening, although this difference was not statistically significant (p = 0.19) (Table 2). Stage I colorectal cancer was more common in patients with MS (29.6%) compared to those without MS (19.0%), but this difference was not statistically significant (p > 0.10). The median colorectal cancer diagnostic interval in patients with MS was 96 days, which was higher than the median diagnostic interval in patients without MS (72 days), although this difference was not statistically significant (p = 0.47). Among those who waited the longest for their diagnosis (the 90th percentile), the diagnostic interval in patients with MS was 292 days, which was shorter than that observed in patients without MS (331 days). Figure 2B further documents the colorectal cancer diagnostic interval, showing longer intervals in patients with MS than without MS.

Table 3 documents the relationships among our 3 outcomes in patients with colorectal cancer. There were no differences in stage (p = 0.57) or diagnostic interval (p = 0.21) between screen-detected and symptomatic patients. The diagnostic interval was associated with stage at diagnosis, with shorter intervals in patients with more advanced stage cancer (p = 0.009).

In adjusted analyses, the odds of colorectal cancer being detected through screening was 48% lower in patients with MS, although the 95% CI includes 1 and is wide, reflecting the small sample size (Table 4). The odds of being diagnosed with stage I cancer were twice as high in patients with MS (OR 2.11 [95% CI 1.03, 4.30]), even after adjustment by diagnostic

Figure 2 Smoothed Density Plot (Kernel Distribution) and Histogram Overlay of the Diagnostic Interval in the Patients With MS and Controls



(A) Breast cancer. (B) Colorectal cancer. MS = multiple sclerosis.

route. These results were similar in sensitivity analyses excluding those with missing stage. The median colorectal cancer diagnostic interval was longer for patients with MS, although the CIs include a difference of 0 days and are wide due to small sample size. There is some indication that among those who waited the longest (90th percentile) the interval is shorter for patients with colorectal cancer with MS, but the results are not statistically significant. We further adjusted this association by disability status given its association with MS (Table 1) and diagnostic interval (the median interval was 170 in those with a disability compared to 71 days in those without a disability [$p = 0.01$]). The (nonstatistically significant) difference attenuated from 21 days (95% CI −9.2, 51.2) to 11 days (95% −21.4, 43.6).

Discussion

Looking at 3 interrelated outcomes characterizing the cancer diagnostic process, we found that persons with MS who develop breast cancer are less likely to have the cancer detected through screening than are persons without MS, and some of this effect is explained by higher disability rates in patients with MS. The screening difference did not translate to higher stage at diagnosis in breast cancer, and conversely, patients with MS and colorectal cancer were more likely to have stage I cancer. The median length of time to be diagnosed did not vary in those with and without MS, although our results indicate it may be longer in colorectal cancer, a finding that needs further study in a larger population. At the extreme of

Table 3 Interrelationships Between Outcomes

	Diagnostic route by stage and by diagnostic interval				*p* Value
	Screened		**Symptomatic**		
Breast cancer	632		1755		
Cancer stage					
I	387 (61.2)		350 (31.2)		<0.0001
II	189 (29.9)		456 (40.6)		
III	38 (6.0)		204 (18.2)		
IV	<6		67 (6.0)		
Unknown	<19		46 (4.1)		
Diagnostic interval, d	29 (17–47)		39 (20–93)		<0.0001
90th %ile	78		178		
	Stage by diagnostic interval				
	I	II	III	IV	
N[a]	737	645	242	70	
Diagnostic interval, d	36 (21–69)	32 (19–65)	29 (13–63)	22 (8–71)	0.0001
90th %ile	149	135	121	130	
	Diagnostic route by stage and by diagnostic interval				***p* Value**
	Screened		**Symptomatic**		
Colorectal cancer	52		218		
Cancer stage					
I	9 (17.3)		48 (22.0)		0.57
II	17 (32.7)		51 (23.4)		
III	14 (26.9)		61 (28.0)		
IV	8 (15.4)		30 (13.8)		
Unknown	4 (7.7)		28 (12.8)		
Diagnostic interval, d	65 (35–125)		89 (30–198)		0.21
90th %ile	155		344		
	Stage by diagnostic interval				
	I	II	III	IV	
N[a]	57	68	75	38	
Diagnostic interval, d	113 (60–220)	72 (31–166)	85 (32–178)	40 (12–130)	0.009
90th %ile	387	324	338	263	

Values are n (%) or median (interquartile range).
[a] Unknown stage is not included (61 breast cancer and 32 colorectal cancer).

the diagnostic interval distribution (90th percentile), patients with MS and breast cancer did not wait as long for their cancer diagnosis once diagnostic route differences were controlled, and point estimates indicate the same may be true for patients with MS and colorectal cancer. Less cancer detection through screening in patients with MS compromises control of the cancer, which can adversely affect survival.[1,2,4-6]

A higher likelihood of having disability in patients with MS explained some of the breast cancer MS–diagnostic route association that we observed and some of the colorectal cancer MS–diagnostic interval association (which was not statistically significant). MS-related disability increases with age,[32] as does cancer occurrence, and increasing mobility impairment within the MS population is associated with less

Table 4 Association Between Multiple Sclerosis and Diagnostic Route (Screened Vs Symptomatic) and Multiple Sclerosis and Cancer Stage (Stage I Vs Other, Which Includes Missing Stage)

	Breast cancer		Colorectal cancer	
	OR	95% CI	OR	95% CI
Diagnostic route				
Unadjusted	0.69	0.53, 0.89	0.57	0.24, 1.34
Adjusted[a]	0.68	0.52, 0.88	0.52	0.21, 1.28
Cancer stage				
Unadjusted	0.82	0.65, 1.04	1.80	0.91, 3.53
Adjusted[a]	0.81	0.64, 1.04	2.11[b]	1.03, 4.30
Adjusted[a] + diagnostic route	0.89	0.69, 1.15	2.10[b]	1.03, 4.28
	Breast cancer		**Colorectal cancer**	
	Median (95% CI)	**90th %ile (95% CI)**	**Median (95% CI)**	**90th %ile (95% CI)**
Diagnostic interval				
Unadjusted	1.0 (−3.4, 5.4)	−24.0 (−54.7, 6.7)	17.0 (−29.2, 63.2)	−39.0 (−177.1, 99.1)
Adjusted[a]	0.9 (−3.7, 5.6)	−16.7 (−39.0, 5.7)	21.0 (−9.2, 51.2)	−10.4 (−111.9, 91.1)
Adjusted[a] + diagnostic route	−0.3 (−5.1, 4.5)	−18.5 (−34.8, −2.2)	21.0 (−6.4, 48.4)	−0.6 (−97.3, 96.0)
Adjusted[a] + diagnostic route + cancer stage	−0.5 (−4.9, 3.9)	−17.1 (−35.1, 0.8)	12.8 (−16.4, 42.0)	−77.2 (−170.1, 15.7)

Abbreviation: OR = odds ratio.
Diagnostic interval difference in days (95% CI) for patients with multiple sclerosis (at the median and at the 90th percentile of the interval distribution).
[a] Adjusted for age, sex (colorectal only), diagnosis year, income quintile, urban/rural residence, and Elixhauser comorbidity score.
[b] Statistically significant results were similar in sensitivity analyses excluding those with missing stage (adjusted OR 2.20 [95% CI 1.06, 4.56]) and adjusted with diagnostic route (OR 2.16 [95% CI 1.04, 4.52]).

access to mammography.[10] Our disability indicator identified 21.2% of the patients with MS and breast cancer and 33.3% of the patients with MS and colorectal cancer as having disability based on the need for home care services or long-term care. This does not capture individuals with milder disability or with sufficient social supports not to require these services. Further investigation is warranted regarding the role of MS-related disability on screening detection of cancer.

The cancer diagnostic route taken by patients with MS was previously unknown; however, less breast and colorectal cancer screening detection has been observed in other populations with high comorbid disease burden,[7,33] and less cancer screening has been documented in the broader MS population.[8-10,34] Patients with MS and severe disability are less likely to have annual mammograms and screening colonoscopies over age 50 years.[34] Similarly, 48% of patients with MS over age 50 years in New York and New Jersey were not having yearly mammograms[8] and patients with MS in Manitoba were 4.8%–5.2% less likely to have regular mammography compared to matched controls.[9]

A study from British Columbia, Canada, showed larger tumor size in patients with MS and breast, prostate, colorectal, or lung cancer, with overall differences driven more by lung and colorectal cancer.[35] A Danish study observed larger tumor size in patients with MS and breast cancer vs patients without MS with breast cancer.[36] More broadly, variability in the direction of breast cancer stage associations with different comorbid diseases has been observed,[14] with patients with cardiovascular disease, gastrointestinal disease, or nonmalignant benign breast disease having reduced odds of advanced breast cancer and patients with diabetes, psychiatric disorders, or hematologic disorders having increased odds of advanced breast cancer. We did not observe an association between MS and breast cancer stage. This could be a true finding, consistent with the breast cancer subset in the British Columbia study,[35] or using stage I as our measure of early-stage cancer may not have been granular enough. Stage I includes tumors up to 2 cm, which could have masked some differences between the patients with and without MS within that tumor size range as the higher use of screening in the patients without MS group likely resulted in more tumors <1 cm. In contrast to our breast cancer results, we observed more stage I colorectal cancer in patients with MS. There is a high occurrence of bowel symptoms and comorbid functional gastrointestinal disorders in patients with MS,[37,38] which could lead to shared symptoms with colorectal cancer and increased gastrointestinal investigations.

In colorectal cancer, some evidence of an association between the length of the diagnostic interval and comorbidity exists.[39,40] Two mechanisms for the role of comorbidity on colorectal

cancer diagnostic delay have been postulated: comorbidities unrelated to cancer were considered competing demands and those that shared symptoms with colorectal cancer were considered alternative explanations.[41] Similarly, we observed a longer median diagnostic interval in the patients with MS and colorectal cancer, although the difference was not statistically significant. When we controlled for stage, the interval difference was reduced. This was likely due to more stage I in the patients with MS, as patients with a less obvious cancer often have longer diagnostic intervals.[23]

If there are compromised cancer diagnostic processes in MS, this appears to be manifesting largely through fewer screen-detected cancers. Our screening results in patients with MS and cancer mirror the cancer screening experience in the whole MS population, so the reasons for less provision of preventive care services to patients with MS need to be better understood. Several potential explanations for diagnostic neglect in patients with MS have been proposed.[35] Relevant to our screening-related findings, possible explanations are competing demands on primary care physicians' time and functional limitations to accessing cancer surveillance programs. In a qualitative study of patients with MS and mobility limitations, reasons for not accessing mammography included transportation barriers, difficulty positioning for the examination, and health care provider attitudes.[42] Psychiatric comorbidity has not been associated with lower screening rates in patients with MS.[9] In the broader literature, screening recommendations from a health care provider were associated with higher screening rates and the most common screening barrier for those with a disability was reported as difficulty getting an appointment.[43] A 2016 systematic review[44] found that barriers to breast cancer screening for women with disability included health insurance, health workers, and physical access barriers.

The cancer diagnostic experience of patients with MS is not well-documented and the interrelationships of diagnostic route, stage, and the length of the diagnostic process are not often considered. By studying these 3 aspects of the diagnostic process together, we isolated cancer screening of patients with MS as a topic for further investigation. This finding in conjunction with previously documented survival disparities[1,2] suggests that disparities in the care of patients with MS need to be addressed. Other design strengths of this population-based study include robust calculation of the diagnostic interval, control for important potential confounders, and the use of sensitivity analyses to assess for any effect of missing stage on our results.

This study should be interpreted in the context of several limitations. Our colorectal cancer population was small due to data availability constraints. We included this other cancer site as a comparator and those findings differed, underscoring the need to consider cancer sites separately. Future work in larger populations investigating differences in diagnostic processes for colorectal cancer would be beneficial. Our calculation of the diagnostic interval did not include the interval from first symptom awareness to first related health care visit. Nonrecognition of the seriousness of cancer symptoms can manifest in longer patient intervals in breast and colorectal cancer.[45] People experiencing marginalization due to their race or ethnicity have different access to cancer screening, and this may be exacerbated among people with MS. Race and ethnicity data were not available for this study. Future research should focus on the intersection between race and MS disease status in understanding comorbid disease outcomes, including cancer.

In the context of improved outcomes and increasing life expectancy for patients with MS, comprehensive health care that includes attention to their risk of other chronic diseases and the quality of care for those diseases needs to be ensured. Among patients with MS and cancer, we observed reduced use of screening to detect breast cancer. MS-related disability may be preventing people from getting mammograms and colonoscopies. Understanding the pathways to earlier detection in both cancers is critical to developing and planning interventions to ameliorate outcomes for people with MS and cancer.

Acknowledgment

This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). Parts of this material are based on data and information compiled and provided by Ontario Health (OH) and the Canadian Institute for Health Information (CIHI). The analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not necessarily reflect those of the funding or data sources; no endorsement is intended or should be inferred. The authors thank IQVIA Solutions Canada Inc. for use of their Drug Information File.

Study Funding

This study was funded by the MS Society of Canada (EGID 3463). R.A.M. is supported by the Waugh Family Chair in Multiple Sclerosis and a Manitoba Research Chair from Research Manitoba.

Disclosure

P. Groome receives research funding from the Multiple Sclerosis Society of Canada. C. Webber has no disclosures relevant to the manuscript. C. Maxwell is supported by a University Research Chair (University of Waterloo) and receives funding from CIHR, Canadian Frailty Network, Multiple Sclerosis Society of Canada, CMSC, Ontario Neurodegenerative Disease Research Initiative Phase 2, Velux Stiftung, Queens University, and PSI Foundation. C. McClintock reports no disclosures relevant to the manuscript. D. Seitz receives research funding from CIHR, the MS Society of Canada, and the University of Calgary and is the site investigator for a clinical trial sponsored by Hoffman La Roche. A. Mahar receives research funding from the Canadian Cancer Society, CIHR, MS Society of Canada, Ontario Institute for Cancer Research, Social Sciences and Humanities Research Council, Children's

Hospital Research Institute of Manitoba, Veterans Affairs Canada, Sherif Hanna Surgical Oncology Research Fund at Sunnybrook Health Sciences Centre, Terry Fox Research Institute, Canada Foundation for Innovation, Research Manitoba, the True Patriot Love Foundation, and the University of Manitoba. R.A. Marrie receives research funding from CIHR, Research Manitoba, Multiple Sclerosis Society of Canada, Multiple Sclerosis Scientific Foundation, Crohn's and Colitis Canada, National Multiple Sclerosis Society, CMSC, the US Department of Defense, Roche, Biogen, and the Government of Alberta and is supported by the Waugh Family Chair in Multiple Sclerosis. Go to Neurology.org/N for full disclosures.

Publication History

Received by *Neurology* July 13, 2021. Accepted in final form January 21, 2022.

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References

1. Marrie RA, Maxwell C, Mahar A, et al. Breast cancer survival in multiple sclerosis: a matched cohort study. *Neurology.* 2021;97(1):e13-e22.
2. Marrie RA, Maxwell C, Mahar A, et al. Colorectal cancer survival in multiple sclerosis: a matched cohort study. *Neurology.* 2021;97(14):e1447-e1456.
3. Neal RD, Tharmanathan P, France B, et al. Is increased time to diagnosis and treatment in symptomatic cancer associated with poorer outcomes? Systematic review. *Br J Cancer.* 2015;112(S1):S92-S107.
4. Plevritis SK, Munoz D, Kurian AW, et al. Association of screening and treatment with breast cancer mortality by molecular subtype in US women, 2000-2012. *JAMA.* 2018; 319(2):154-164.
5. Tabár L, Dean PB, Chen TH, et al. The incidence of fatal breast cancer measures the increased effectiveness of therapy in women participating in mammography screening. *Cancer.* 2019;125(4):515-523.
6. Maida M, Macaluso FS, Ianiro G, et al. Screening of colorectal cancer: present and future. *Expert Rev Anticancer Ther.* 2017;17(12):1131-1146.
7. Spolverato G, Capelli G, Battagello J, et al. More favorable short and long-term outcomes for screen-detected colorectal cancer patients. *Front Oncol.* 2021;11:620644.
8. Shabas D, Weinreb H. Preventive healthcare in women with multiple sclerosis. *J Womens Health Gend Based Med.* 2000;9:389-395.
9. Marrie RA, Walld R, Bolton JM, et al. Effect of comorbid mood and anxiety disorders on breast and cervical cancer screening in immune-mediated inflammatory disease. *PLoS ONE.* 2021;16(8):e0249809.
10. Cheng E, Myers L, Wolf S, et al. Mobility impairments and use of preventive services in women with multiple sclerosis: observational study. *BMJ.* 2001;323(7319):968-969.
11. Gospodarowicz MK, O'Sullivan B, Sobin LH, eds. *Prognostic Factors in Cancer*, 3rd ed. John Wiley & Sons, Inc.; 2006.
12. Corley DA, Jensen CD, Quinn VP, Doubeni CA, et al. Association between time to colonoscopy after a positive fecal test results and risk of colorectal cancer and cancer stage at diagnosis. *JAMA.* 2017;317(16):1631-1641.
13. Bjerager MPT, Palshof T, Dahl R, Vedsted P, Olesen F. Delay in diagnosis of lung cancer in clinical practice. *Br J Gen Pract.* 2006;56:863-868.
14. Fleming ST, Pursley HG, Newman B, Pavlov D, Chen K. Comorbidity as a predictor of stage of illness for patients with breast cancer. *Med Care.* 2005;43(2):132-140.
15. Go Canada. Canada Health Act. Minister of Justice; 1985.
16. Groome PA, Webber C, Whitehead M, et al. Determining the cancer diagnostic interval using administrative health care data in a breast cancer cohort. *JCO Clin Cancer Inform.* 2019;3(3):1-10.
17. Webber C, Flemming JA, Birtwhistle R, Rosenberg M, Groome PA. Colonoscopy resource availability and its association with the colorectal cancer diagnostic interval: a population-based cross-sectional study. *Eur J Cancer Care.* 2020;29(1):e13187.
18. Robles SC, Marrett LD, Clarke EA, Risch HA. An application of capture-recapture methods to the estimation of completeness of cancer registration. *J Clin Epidemiol.* 1988;41(5):495-501.
19. Brierley JD, Srigley JR, Yurcan M, et al. The value of collecting population-based cancer stage data to support decision-making at organizational, regional and population levels. *Healthc Q.* 2013;16(3):27-33.
20. Al-Sakran LH, Marrie RA, Blackburn DF, Knox KB, Evans CD. Establishing the incidence and prevalence of multiple sclerosis in Saskatchewan. *Can J Neurol Sci.* 2018;45:295-303.
21. Jiang L, Gilbert J, Langley H, Moineddin R, Groome PA. Effect of specialized diagnostic assessment units on the time to diagnosis in screen-detected breast cancer patients. *Br J Cancer.* 2015;112(11):1744-1750.
22. Jiang L, Gilbert J, Langley H, Moineddin R, Groome PA. Is being diagnosed at a dedicated breast assessment unit associated with a reduction in the time to diagnosis for symptomatic breast cancer patients? *Eur J Cancer Care.* 2018;27(4):e12864.
23. Tørring ML, Frydenberg M, Hansen RP, Olesen F, Vedsted P. Evidence of increasing mortality with longer diagnostic intervals for five common cancers: a cohort study in primary care. *Eur J Cancer.* 2013;49(9):2187-2198.
24. Tørring ML, Murchie P, Hamilton W, et al. Evidence of advanced stage colorectal cancer with longer diagnostic intervals: a pooled analysis of seven primary care cohorts comprising 11 720 patients in five countries. *Br J Cancer.* 2017;117(6):888-897.
25. Webber C, Whitehead M, Eisen A, Holloway CMB, Groome PA. Breast cancer diagnosis and treatment wait times in specialized diagnostic units versus usual care. *Curr Oncol.* 2020;27(4):e377-e385.
26. Webber C, Whitehead M, Eisen A, Holloway CMB, Groome PA. Factors associated with waiting time to breast cancer diagnosis among symptomatic breast cancer patients: a population-based study from Ontario, Canada. *Breast Cancer Res Treat.* 2021; 187(1):225-235.
27. Sobin LH, Gospodarowicz M, Wittekind C. *The TNM Classification of Malignant Tumours*, 7th ed. Wiley-Blackwell; 2009.
28. Shewart WA. *Economic Control of Quality of Manufactured Product.* Van Nostrand Reinhold; 1931.
29. Page ES. Continuous inspection schemes. *Biometrika.* 1954;41:100-115.
30. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care.* 1998;36(1):8-27.
31. Turcotte LA, Marrie RA, Patten SB, Hirdes JP. Clinical profile of persons with multiple sclerosis across the continuum of care. *Can J Neurol Sci.* 2018;45:188-198.
32. Trojano M, Liguori M, Bosco Zimatore G, et al. Age-related disability in multiple sclerosis. *Ann Neurol.* 2002;51(4):475-480.
33. Yuan Y, Li M, Yang J, et al. Factors related to breast cancer detection mode and time to diagnosis in Alberta, Canada: a population-based retrospective cohort study. *BMC Health Serv Res.* 2016;16:65.

34. Dobos K, Healy B, Houtchens M. Access to preventive health care in severely disabled women with multiple sclerosis. *Int J MS Care.* 2015;17:200-205.
35. Kingwell E, Bajdik C, Phillips N, et al. Cancer risk in multiple sclerosis: findings from British Columbia, Canada. *Brain.* 2012;135(Pt 10):2973-2979.
36. Nielsen NM, Rostgaard K, Rasmussen S, et al. Cancer risk among patients with multiple sclerosis: a population-based register study. *Int J Cancer.* 2006;118(4):979-984.
37. Nortvedt MW, Riise T, Frugård J, et al. Prevalence of bladder, bowel and sexual problems among multiple sclerosis patients two to five years after diagnosis. *Mult Scler.* 2007;13:106-112.
38. Marrie RA, Leung S, Tyry T, Cutter GR, Fox R, Salter A. Functional gastrointestinal disorders negatively affect health-related quality of life in MS. *Neurol Clin Pract.* 2019;9(5):381-390.
39. Webber C, Jiang L, Grunfeld E, Groome PA. Identifying predictors of delayed diagnoses in symptomatic breast cancer: a scoping review. *Eur J Cancer Care.* 2017;26(2):e12483.
40. Golding HW, Webber C, Groome PA. Factors contributing to time to diagnosis in symptomatic colorectal cancer: a scoping review. *Eur J Cancer Care.* 2020;30(3):e13397.
41. Mounce LTA, Price S, Valderas JM, Hamilton W. Comorbid conditions delay diagnosis of colorectal cancer: a cohort study using electronic primary care records. *Br J Cancer.* 2017;116(12):1536-1543.
42. Todd A, Stuifbergen A. Barriers and facilitators related to breast cancer screening: a qualitative study of women with multiple sclerosis. *Int J MS Care.* 2011;13:49-56.
43. Steele CB, Townsend JS, Courtney-Long EA, Young M. Prevalence of cancer screening among adults with disabilities, United States, 2013. *Prev Chronic Dis.* 2017;14:E09.
44. Ramjan L, Cotton A, Algoso M, Peters K. Barriers to breast and cervical cancer screening for women with physical disability: a review. *Women Health.* 2016;56(2):141-156.
45. Macleod U, Mitchell ED, Burgess C, Macdonald S, Ramirez AJ. Risk factors for delayed presentation and referral of symptomatic cancer: evidence for common cancers. *Br J Cancer.* 2009;101(suppl 2):S92-S101.