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Cancer Risk Among Patients With Multiple Sclerosis

A 10-Year Nationwide Retrospective Cohort Study

Chloe Pierret, MSc, Aurelien Mulliez, MSc, Christine Le Bihan-Benjamin, MD, PhD, Xavier Moisset, MD, PhD, Philippe-Jean Bousquet, MD, PhD, and Emmanuelle Leray, PhD

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Correspondence

Chloe Pierret
chloe.pierret@ehesp.fr

Abstract

Background and Objectives

Previous literature has been diverging on cancer risk in people with multiple sclerosis (PwMS). Therefore, this study compared the risk of cancer in PwMS and a matched sample from the French general population.

Methods

This 10-year nationwide retrospective matched cohort study (2012–2021) used data from the national French administrative health care database (99% coverage of the French population) to determine the time to the first incident cancer. PwMS were identified using their long-term disease (LTD) status, hospitalizations, and multiple sclerosis (MS)-specific drug reimbursements. The control population was matched 4:1 on age, sex, residence, insurance scheme, and cohort entry date. Participants were included if they had no history of cancer in the 3 years before inclusion. Patients with cancer were identified through LTD status, hospitalizations, chemotherapy, radiotherapy, or prostate cancer-specific drug reimbursements. Overall and cancer location-specific hazard ratios (HRs) for the first incident cancer were obtained from Fine and Gray models, and age- and sex-stratified estimates were reported. Participation in cancer screening through the 3 national programs (breast, colorectal, and cervical) were compared between groups.

Results

Cancer incidence was 799 per 100,000 person-years (PYs) ($n = 8,368$) among the 140,649 PwMS and 736 per 100,000 PYs ($n = 31,796$) among the 562,596 matched controls (70.8% of women; follow-up: 7.6 ± 3.2 years). A small overall risk increase was observed for PwMS (HR 1.06, 95% CI 1.03–1.08), mostly in women (HR 1.08, 95% CI 1.05–1.11). Risk varied by cancer types and was lower for prostate (HR 0.80, 95% CI 0.73–0.88), breast (HR 0.91, 95% CI 0.86–0.95), and colorectal (HR 0.90, 95% CI 0.84–0.97) cancer and higher for bladder (HR 1.71, 95% CI 1.54–1.89), brain (HR 1.68, 95% CI 1.42–1.98), and cervical (HR 1.24, 95% CI 1.12–1.38) cancer in PwMS. Cancer risk was higher in PwMS younger than 55 years (HR 1.20, 95% CI 1.15–1.24) but decreased in PwMS aged 65 years and older (HR 0.89, 95% CI 0.85–0.94). This trend was found in all cancer locations. There were fewer PwMS getting screened than controls (all programs), with a particularly pronounced difference among those aged 65 years and older.

Discussion

Cancer risk was slightly increased in PwMS, particularly for urogenital cancers, possibly due to surveillance bias. Risk fluctuated depending on age, perhaps due to varying generational screening practices (i.e., diagnosis neglect in the older PwMS) and risk factors.

From the EHESP, CNRS, Inserm, ARENES UMR 6051, RSMS U 1309 (C.P., E.L.), Rennes University; Clermont-Ferrand University Hospital Center (A.M., X.M.); Survey, Data Science and Assessment Division (C.L.B.-B., P.-J.B.), French National Cancer Institute-InCA, Boulogne-Billancourt; and NeuroDol U1107 (X.M.), Clermont Auvergne University, Clermont-Ferrand, France.

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e209885(1)

Glossary

DMT = disease-modifying therapy; EHESP = French School of Public Health; HPV = human papillomavirus; HR = hazard ratio; ICD-10 = *International Classification of Diseases, 10th Revision*; INCa = National French Cancer Institute; IRR = incidence rate ratio; LTD = long-term disease; MS = multiple sclerosis; NMOSD = neuromyelitis optica spectrum disorder; PwMS = people with multiple sclerosis; PY = person-year; SNDS = *Système National des Données de Santé*.

Introduction

Multiple sclerosis (MS), a demyelinating, inflammatory autoimmune disorder of the CNS, is estimated to affect 2.8 million individuals worldwide and 130,000 in France.^{1,2} It is often diagnosed between the age of 25 and 35 years and particularly affects women.³ Survival has improved but remains lower than in the general population by 5–10 years.⁴ The inflammatory nature of MS, alongside potential toxicity associated with new disease-modifying therapies (DMTs), and the high prevalence in this population for suspected cancer risk factors, such as hypertension and chronic lung diseases, suggest a potential excess risk of cancer.⁵ There is no consensus, and some pre-DMT era studies found a decreased risk.^{6–8} Conversely, more recent studies reported no association^{9–21} or increased risk.^{22–25} A recent French study found a 30% increase in cancer risk in people with MS (PwMS) compared with the matched general population.²³ These discrepancies can be attributed to differences in study populations and methodologies. Moreover, the limited number of people with less frequent tumor types resulted in lack of power and inability to perform subgroup analyses. In previous studies, risk differed by tumor type. The risk of brain or urological cancers was found to be most often increased and that of prostate cancer decreased in PwMS compared with the general population.^{8,11,14,26} The French Society for Multiple Sclerosis currently recommends that PwMS follow the general population screening guidelines.²⁷ However, some evidence suggests that cancer screening adherence might be lower in PwMS, especially those with advanced disability.²⁸

In this study, we assessed cancer risk in PwMS compared with the general population through a retrospective matched cohort study using data from the national administrative health care database in France. We also compared breast, cervical, and colorectal cancer screening behaviors between these groups.

Methods

Study Design and Data Source

Data Source

The *Système National des Données de Santé* (SNDS) is the French national administrative health care database that covers approximately 66 million inhabitants (~99% of the French population). It combines data from hospitals (private and public), inpatient and outpatient services, and drug

prescription reimbursements and is increasingly used for epidemiologic purposes.²⁹

In this database, all hospitalization entry and exit dates are recorded, as well as the relevant *International Classification of Diseases, 10th Revision* (ICD-10) diagnosis codes.²⁹ Each clinical procedure is recorded through the *Classification commune des actes médicaux*, a nationally standardized classification of medical procedures. Moreover, in France, since 1945, a long-term disease (LTD) status can be requested for 30 chronic diseases (e.g., MS, cancer, and diabetes) that require expensive or long treatments. Sociodemographic data are also available: date of birth, sex, insurance scheme, and department of residence. Because SNDS primary goal is to measure health care expenditures, reports of consultations with clinicians and laboratory test results are not available and identification algorithms are needed to identify diseases.

Study Design

For this 10-year retrospective cohort study, SNDS data from 2012 to 2021 were used. PwMS were included in the cohort with the index date as the latest date between the following: January 1, 2012 (start of the study period), MS identification date, or their 18th birthday date. Eligible PwMS had no history of cancer in the 3 years preceding their index date. Each person with MS was matched up exactly by birth year, sex, residence at entry, and insurance scheme at entry to 4 controls that were randomly selected without replacement from the general population and assigned the same index date as their matched PwMS (eFigure 1). Similarly, eligible controls had no history of cancer in the 3 years before their assigned index date and had no MS-related care consumption (MS hospitalization, MS-LTD, MS drug reimbursement) during the entire study period. All individuals were followed until the first incident cancer, death, or December 31, 2021 (end of the study period), whichever came first. Covariates were measured at the index date unless otherwise specified. Indicators of cancer screening for the 3 French national screening programs were retrieved and compared between groups (e.g., mammography for breast cancer, Pap smear or human papillomavirus [HPV] test for cervical cancer, and occult blood in stool detection test for colorectal cancer).³⁰

Study Population

MS Identification

PwMS were identified based on the presence of at least one of the following criteria: (1) LTD for MS (MS-LTD), (2)

hospitalization for MS, and (3) MS-specific drug reimbursements (β -interferon, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, natalizumab, ocrelizumab, ponesimod, and teriflunomide).^{2,31} Information on hospitalizations and DMTs are available in the SNDS database from January 1, 2009, and LTD status since its introduction. MS-LTD status and hospitalization for MS were identified by the “G35” ICD-10 code. To ensure the specificity of our case definition, individuals were not included if they met the 3 following criteria: (1) did not have the MS-LTD status, (2) had only 1 hospitalization for MS, and (3) did not have any MS-specific drug reimbursement. In addition, individuals with (1) no MS-LTD status, (2) no MS-hospitalization, and (3) only 1 MS-specific drug reimbursement over the observation period were not included. Because the similar clinical picture of neuromyelitis optica spectrum disorder (NMOSD) and MS can lead to a false-positive MS diagnosis, individuals with at least 1 NMOSD hospitalization (ICD-10 code: G36), no MS-LTD status, and no MS-specific drug reimbursement were excluded. This identification algorithm was defined in collaboration with neurologists and MS experts and adapted from a previous study.³¹ Therefore, its exact validity remains to be determined.

MS identification date was defined as the earliest available date between MS hospitalization, MS-LTD status declaration, and MS-specific drug reimbursement. Therefore, it did not correspond exactly to MS onset or MS diagnosis. All individuals aged 18 years and older, alive on January 1, 2012, who met the inclusion and exclusion criteria were included.

Primary Outcome: All Cancer

Our primary outcome measure was first incident cancer (ICD-10: C* or D0*). Because the cancer diagnosis date is not directly available in the SNDS database, we developed an algorithm in collaboration with the National French Cancer Institute (INCa). This algorithm uses a combination of cancer-LTD status, hospitalization records, prostate cancer drug reimbursements,³² radiotherapy, and chemotherapy (eTable 1).³³ The first incident cancer date was defined as the date of the first cancer treatment. If no treatment date was available and only the cancer-LTD status without any subsequent use of care was found, the individual was excluded. To minimize the inclusion of individuals with recurrent cancer, individuals with a hospitalization with the code “personal cancer antecedent” (Z85-) as the first incident cancer identification were excluded. Nonmelanoma skin cancers were not included in our cancer definition because they are not well identified in the SNDS database.

Secondary Outcomes: Selected Cancer Types

The following selected cancer types were defined as secondary outcomes: bladder, brain and CNS, breast, cervical, colorectal, kidney, lung, prostate, and skin (eTable 2). Cancer type was defined as the first cancer site identified through the cancer-LTD status, hospitalization, or drug reimbursement.

Some secondary tumors (i.e., lung, bone, brain and CNS, and liver) can be falsely categorized as primary tumors during the cancer diagnosis process. To minimize this potential classification error, if the first identified location was a “potential” false primary tumor (i.e., lung, bone, brain and CNS, and liver) followed within 6 months by another location, this second location was considered as the primary tumor.

The primary cancer location could not be identified in the following cases: (1) cancer identified only based on chemotherapy or radiotherapy data without any available ICD-10 code; (2) 2 different cancer locations identified simultaneously on the first incident cancer treatment date; and (3) multiple “potential” false primary locations (i.e., lung, bone, brain and CNS, and liver) identified in the first 6 months after the first incident cancer treatment date. In these cases, cancer location was classified as “unknown.”

Cancer Screening

There are 3 national cancer screening programs in France. Since 2004, women aged between 50 and 74 are invited to do a breast cancer screening every 2 years by undergoing a mammography. Similarly, since 2008, men and women aged between 50 and 74 are invited to get screened for colorectal cancer every 2 years through an occult blood in stool test. Finally, since 2018, women between 25 and 65 are invited to participate in the national cervical cancer screening program (every 3 years between 25 and 29; every 5 years between 30 and 65).³⁴

Statistical Analysis

Crude incidence was reported for each group, as well as incidence standardized on age and sex to the 2021 French population. We assessed the association between MS and time to cancer onset using survival methods. Time to onset was computed from index date to cancer onset, and in absence of cancer, time to latest news (death or end of follow-up) was computed and used as censoring. Because cancer appears late in life and PwMS have a lower life expectancy than the general population, we took into account death as a competing risk by implementing a Fine and Gray model.^{4,35}

The overall and location-specific hazard ratios (HRs) were calculated with their 95% CIs. Similarly, when calculating location-specific HRs, death was treated as a competing risk event. Overall and location-specific HRs were calculated by sex and age groups (younger than 55 years, between 55 and 64 years, 65 years and older). Proportional hazard assumption of the Fine and Gray model was assessed graphically using Schoenfeld residuals and the Lin test. In addition, an E-value analysis was performed to assess which magnitude of unmeasured confounding could nullify our estimates.³⁶ Finally, as additional exploratory analysis, cancer mortality rates were retrieved and compared between both groups using a Poisson regression analysis adjusted for sex and age at cancer diagnosis.

Cancer screening indicators (breast, cervical, and colorectal cancer) were summarized for both groups and by sex and age and compared between groups. For each screening program, only individuals eligible for the program for at least 1 day during our observation period were included and they were followed up during their periods of eligibility (breast: women between 50 and 74 years; cervical: women between 25 and 65 years; and colorectal: men and women between 50 and 74 years). Data management was performed using SAS software version 8.3.7 and R version 4.1.2, and statistical analyses were performed with R version 4.1.2.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was conducted at the French School of Public Health (EHESP) that has permanent access to the SNDS database in application of the provisions of Articles R.1461-11 to R.1461-17 of the French Public Health Code and the French Data Protection Authority decision CNIL-2016-316. As permanent SNDS database users, the authors declared the study to the EHESP SNDS registry, which is equivalent to an institutional review board approval.

Data Availability

The SNDS database is the property of the French health insurance system (Caisse Nationale d'Assurance Maladie).

Permission to reuse data can be requested, but it necessitates obtaining previous approval from the regulatory authorities in France. All medical procedures and cancer identification codes are available in eTables 1–3.

Results

Population Characteristics

In total, 140,649 PwMS were included (Figure 1) and were matched with 562,596 controls; 70.8% were women, and the mean age at index date was 46.7 ± 14.5 years. Participants were followed for 7.6 ± 3.2 years, with no major difference between sex or age groups. During the available time frame (i.e., from 3 years preceding cohort entry to the end of follow-up), 58.3% of PwMS received at least 1 reimbursement of MS-specific DMT. At entry, PwMS had more LTDs declared for type 1 diabetes (2.5% vs 1.6%) and depressive episodes (7.2% vs 5.9%), but no difference was observed for hypertension (3.4% vs 3.7%) and chronic ischemic heart disease (2.2% vs 2.5%). During this period, an incident cancer was identified in 8,368 PwMS (5.9%) and 31,796 controls (5.7%) (Table 1). The most common cancer types were breast ($n = 9,754$; 35.8%), colorectal ($n = 2,740$; 10.1%), lung ($n = 1,884$; 6.9%), and cervical ($n = 1,865$; 6.9%) in women and prostate ($n = 3,153$; 24.3%), lung ($n = 1,647$; 12.7%), and colorectal ($n = 1,636$; 12.6%) in men (eTable 4).

Figure 1 Population Selection Flowchart

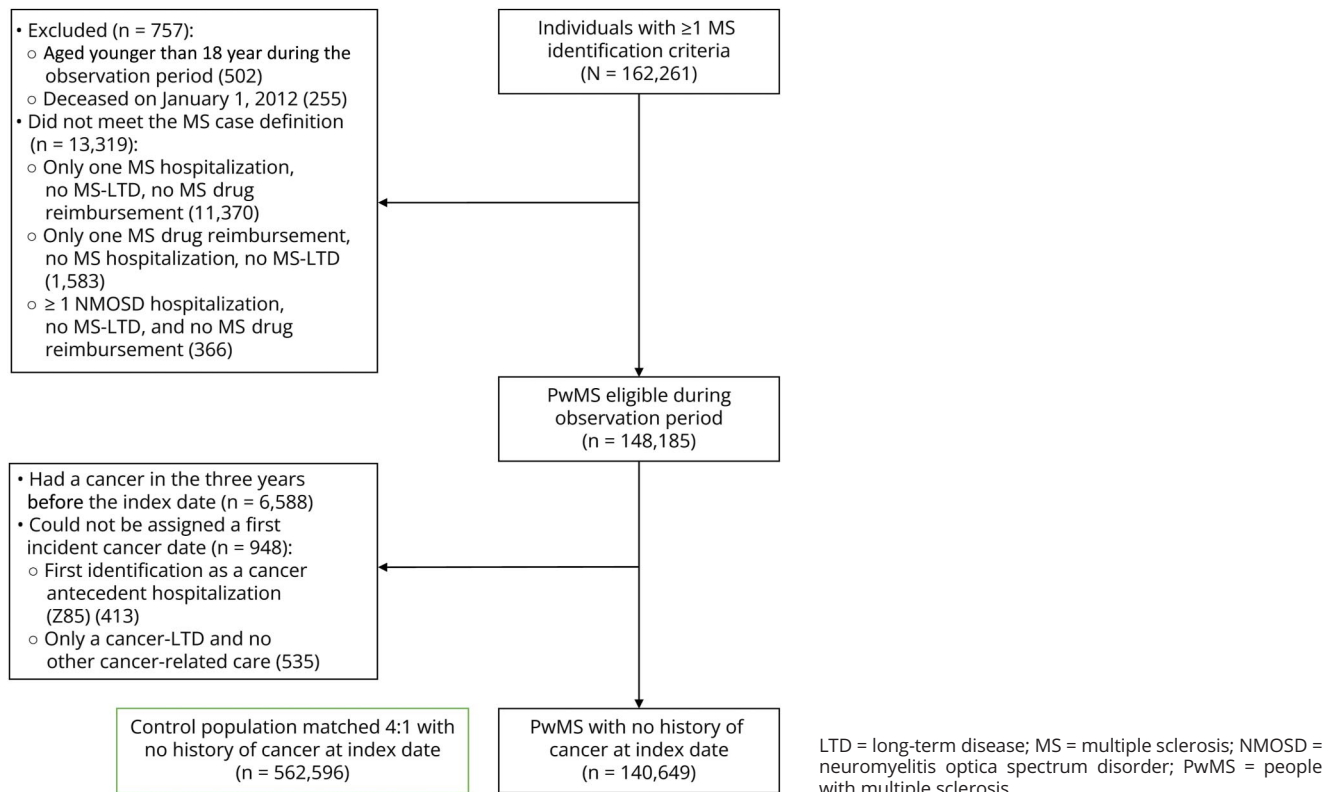


Table 1 Baseline Characteristics

	PwMS (n = 140,649)	Controls (n = 562,596)
Demographics		
Sex, n (%)		
Female	99,629 (70.8)	398,516 (70.8)
Male	41,020 (29.2)	164,080 (29.2)
Age at entry, y, n (%)		
Mean (SD)	46.7 (14.5)	46.7 (14.5)
≤30	20,364 (14.5)	81,456 (14.5)
31–40	30,010 (21.3)	120,040 (21.3)
41–50	35,175 (25.0)	140,700 (25.0)
51–60	29,802 (21.2)	119,208 (21.2)
61–70	17,264 (12.3)	69,056 (12.3)
>70	8,034 (5.7)	32,136 (5.7)
Age at MS identification, y, mean (SD)	40.5 (13.0)	—
Cancer cases, n (%)		
Prostate	523 (6.3)	2,630 (8.3)
Colon-rectum	805 (9.6)	3,571 (11.2)
Breast	1,803 (21.5)	7,951 (25.0)
Lung	703 (8.4)	2,828 (8.9)
Skin	254 (3.0)	919 (2.9)
Kidney	267 (3.2)	923 (2.9)
Cervical	442 (5.3)	1,423 (4.5)
Brain and CNS	202 (2.4)	482 (1.5)
Bladder	512 (6.1)	1,201 (3.8)
Other (incl. unknown)	2,857 (34.1)	9,868 (31.0)
Unknown	804 (9.6)	1,331 (4.2)
Age at first cancer, y, mean (SD)	59.9 (12.9)	61.8 (12.7)
Year of entry, n (%)		
2012	90,806 (64.6)	363,224 (64.6)
2013	5,516 (3.9)	22,064 (3.9)
2014	5,749 (4.1)	22,996 (4.1)
2015	5,659 (4.0)	22,636 (4.0)
2016	5,629 (4.0)	22,516 (4.0)
2017	5,412 (3.8)	21,648 (3.8)
2018	5,527 (3.9)	22,108 (3.9)
2019	5,396 (3.8)	21,584 (3.8)
2020	5,394 (3.8)	21,576 (3.8)
2021	5,561 (4.0)	22,244 (4.0)

Table 1 Baseline Characteristics (continued)

	PwMS (n = 140,649)	Controls (n = 562,596)
Year of exit, n (%)		
2012	977 (0.7)	2,479 (0.4)
2013	1,563 (1.1)	3,628 (0.6)
2014	1,687 (1.2)	3,867 (0.7)
2015	1,788 (1.3)	4,235 (0.8)
2016	1,872 (1.3)	4,492 (0.8)
2017	1,974 (1.4)	4,913 (0.9)
2018	2,075 (1.5)	5,204 (0.9)
2019	2,162 (1.5)	5,527 (1.0)
2020	2,168 (1.5)	5,841 (1.0)
2021	124,383 (88.4)	522,410 (92.9)
Follow-up time, y, mean (SD)	7.4 (3.2)	7.7 (3.2)
Death, n (%)		
Death, n (%)	12,646 (9.0)	22,985 (4.1)
Age at death, y, mean (SD)	67.9 (13.3)	71.3 (14.3)
Comorbidities at entry^a		
LTD number at entry, n (%)^b		
0	107,018 (76.1)	433,067 (77.0)
1	22,901 (16.3)	84,346 (15.0)
2	7,106 (5.1)	29,218 (5.2)
3+	3,624 (2.6)	15,965 (2.8)
Diabetes, n (%)		
Type I	2,836 (2.5)	8,521 (1.6)
Type II	11,112 (9.8)	71,510 (13.4)
Depressive episodes	8,136 (7.2)	31,524 (5.9)
Chronic ischemic heart disease	3,805 (3.4)	19,546 (3.7)
Hypertension	2,493 (2.2)	13,104 (2.5)

Abbreviations: LTD = long-term disease; MS = multiple sclerosis; PwMS = people with multiple sclerosis.

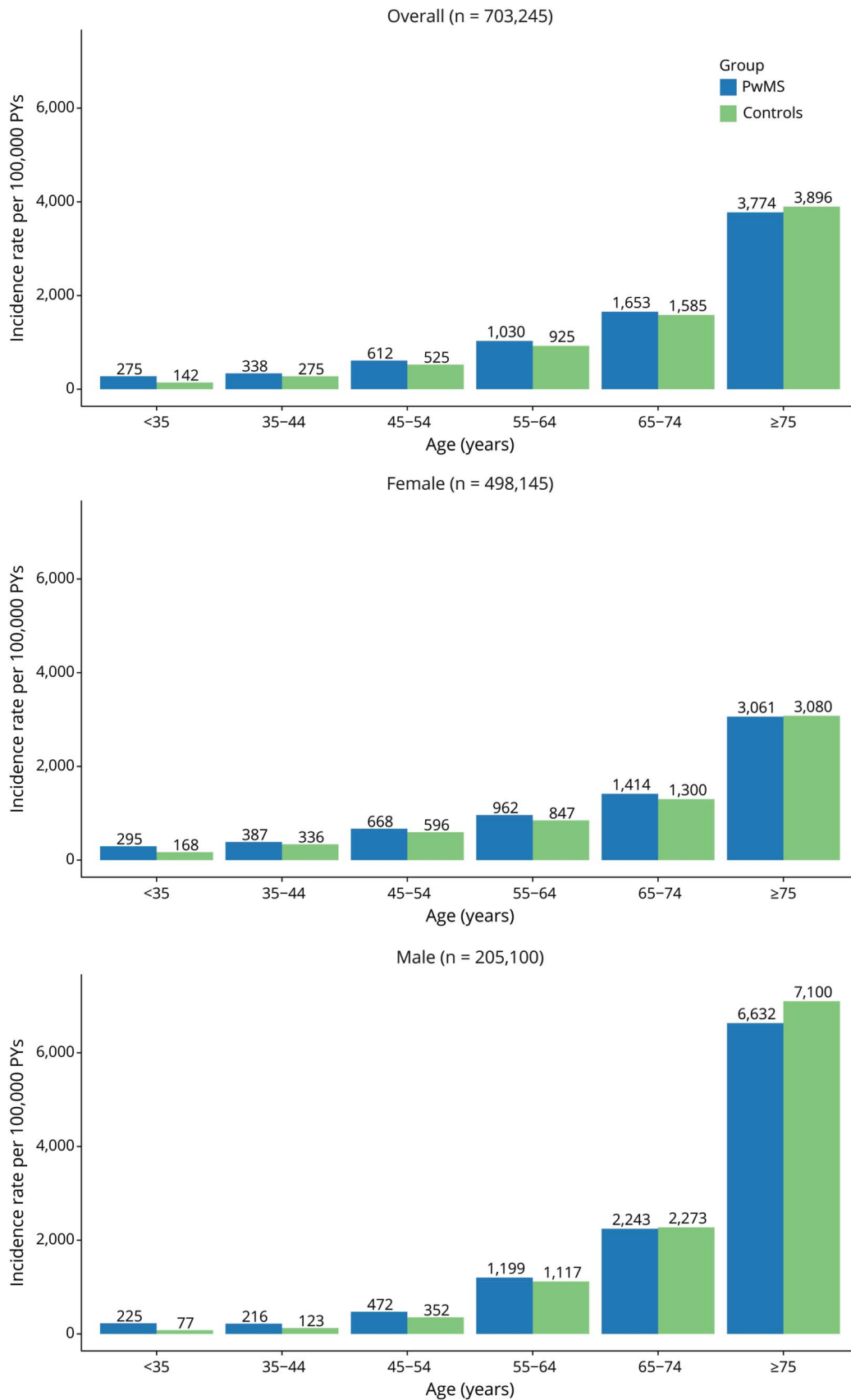
^a All comorbidity data come from the LTD status at entry.

^b Not including cancer, MS, and MS-related LTD status (i.e., demyelinating events).

Cancer Risk in MS

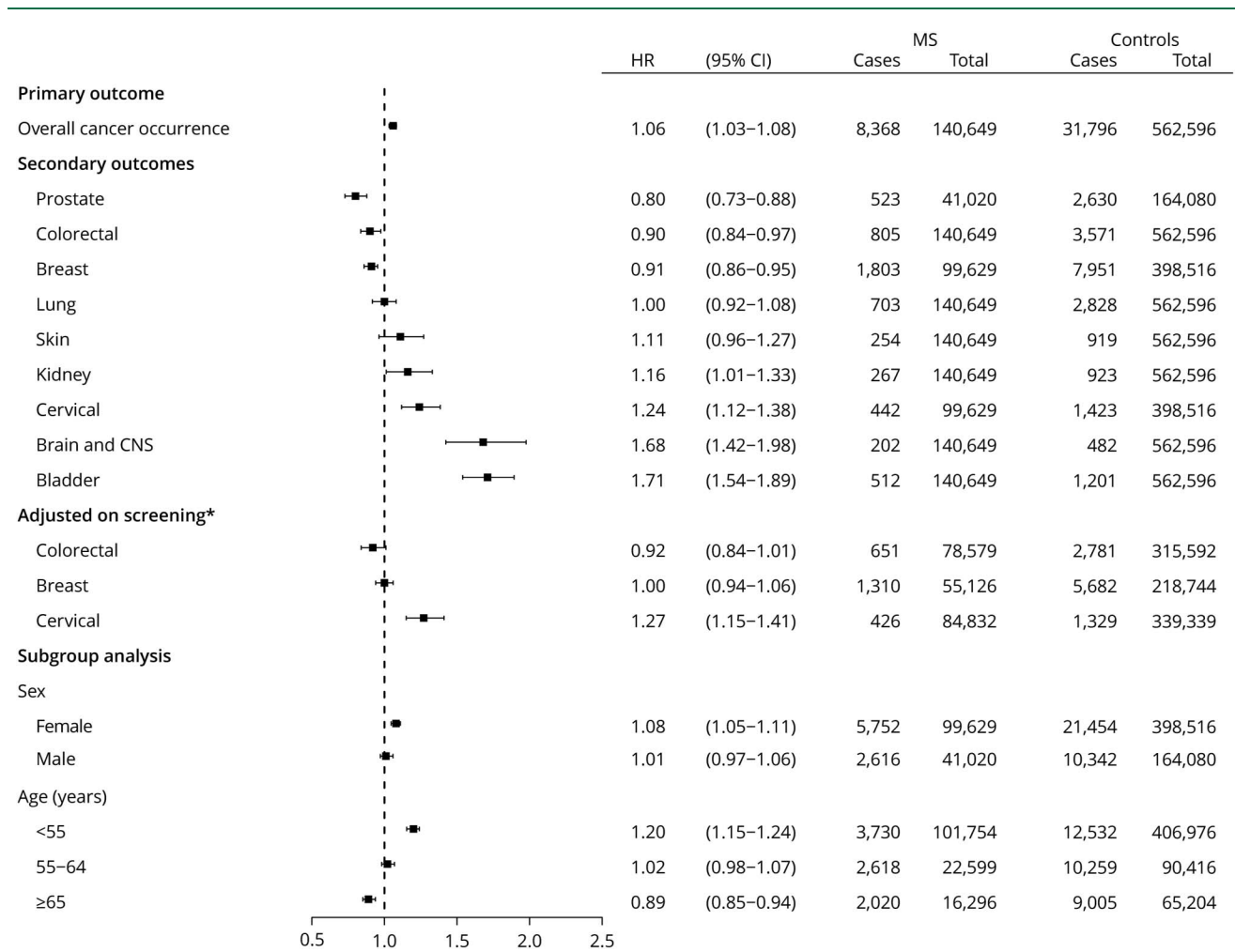
Cancer incidence was 799 per 100,000 person-years (PYs) among the PwMS and 736 per 100,000 PY among the matched controls. The crude cancer incidence, by sex and age, is presented in Figure 2. Cancer incidence standardized by age and sex was 926 per 100,000 PYs (95% CI 898–955) among PwMS and 872 (95% CI 858–886) among the matched controls. Overall, a small increase in risk was observed in PwMS (HR 1.06, 95% CI 1.03–1.08) (Figure 3). However, after stratification by sex, the higher risk was observed only in women (HR 1.08, 95% CI 1.05–1.11 vs HR 1.01, 95% CI

Figure 2 Cancer Incidence: Overall and by Sex in the Different Age Groups (n = 703,245)



PwMS = people with multiple sclerosis; PY = person-year.

Figure 3 Results of the Fine and Gray Model to Assess the Risk of Cancer in People With Multiple Sclerosis Compared With the Matched Control Group From the General Population



HPV = human papillomavirus; HR = hazard ratio; MS = multiple sclerosis. *Colorectal adjusted for blood in stool testing. Breast adjusted for mammography. Cervical adjusted for Pap smear and HPV test. Each analysis was conducted on participants eligible for each screening.

0.97–1.06). Compared with controls, PwMS had a higher risk of bladder (HR 1.71, 95% CI 1.54–1.89), brain and CNS (HR 1.68, 95% CI 1.42–1.98), cervical (HR 1.24, 95% CI 1.12–1.38), and kidney (HR 1.16, 95% CI 1.01–1.33) cancer. Conversely, PwMS had a lower risk of prostate (HR 0.80, 95% CI 0.73–0.88), colorectal (HR 0.90, 95% CI 0.84–0.97), and breast (HR 0.91, 95% CI 0.86–0.95) cancer. Excess risk was only found in PwMS younger than 55 years (HR 1.20, 95% CI 1.15–1.24), and the HR estimates by age showed a linear trend, with a decrease in risk as age at entry increased. E-value analysis is shown in the supplementary data.

Subgroup Analyses

Sex Differences in Cancer Risk

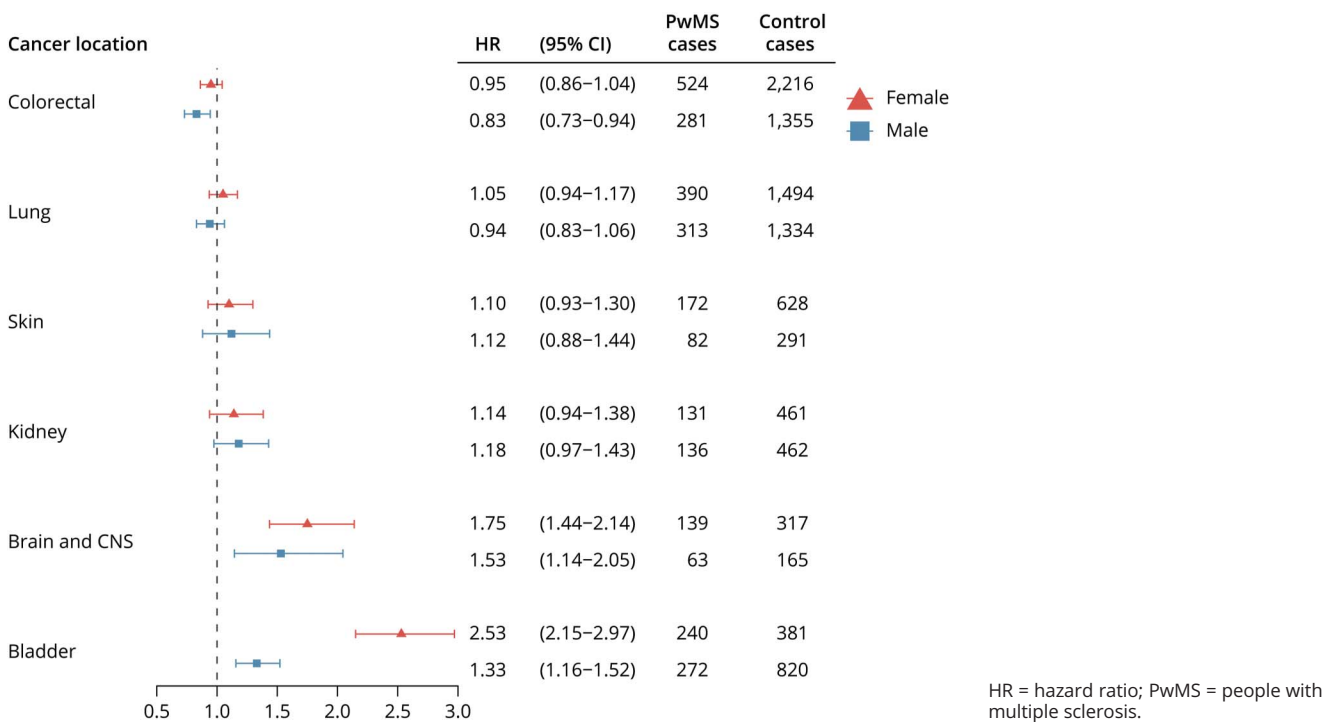
Compared with controls, the overall cancer risk was significantly higher in women than in men with MS, although no sex difference was observed for colorectal, lung, skin, kidney, and brain and CNS tumors (Figure 3). Only the risk of bladder cancer was significantly higher in women than in men (HR

2.53, 95% CI 2.15–2.97 vs HR 1.33, 95% CI 1.16–1.52) (Figure 4).

Age Difference in Cancer Risk

Overall, compared with controls, the cancer risk in PwMS decreased as age increased and the highest HR values were found in the group younger than 55 years at entry (HR 1.20, 95% CI 1.15–1.24) and the lowest in the group aged 65 years and older (HR 0.89, 95% CI 0.85–0.94) (Figure 3). This trend was also observed for each tumor type. In the youngest age group (younger than 55 years), the risk was increased in most types except for prostate, breast, and colorectal cancer (no cancer risk increase) (Figure 5). No cancer type had a reduced risk. Conversely, in the group aged 65 years and older, the risk increased only for bladder cancer (HR 1.44, 95% CI 1.22–1.71). For the other cancer types, risk was either decreased (prostate, breast, colorectal, lung) or unchanged (skin, kidney, cervical, brain and CNS).

Figure 4 Results of the Fine and Gray Model to Assess the Risk of Cancer by Cancer Type in PwMS Compared With the General Population Stratified by Sex



Cancer Screening

Compared with controls, fewer PwMS underwent screening for breast cancer (mammography) (64.9% vs 71.6%, $p < 0.001$), cervical cancer (Pap smear or HPV test) (63.2% vs 64.1%, $p < 0.001$), and colorectal cancer (occult blood in stool test) (34.6% vs 36.9%, $p < 0.001$) (Table 2). In the 3 age groups, cancer screening tended to decrease with age in PwMS but not in controls, leading to a widening of the gap between the 2 groups, regardless of the screening procedure or sex. After adjusting for mammography use, no difference in risk of breast cancer was observed. Similarly, no difference in colorectal cancer risk was observed after adjusting for participation in the screening program. However, an increase in risk was still present in PwMS when adjusting for cervical cancer screening (Figure 3; eTable 5).

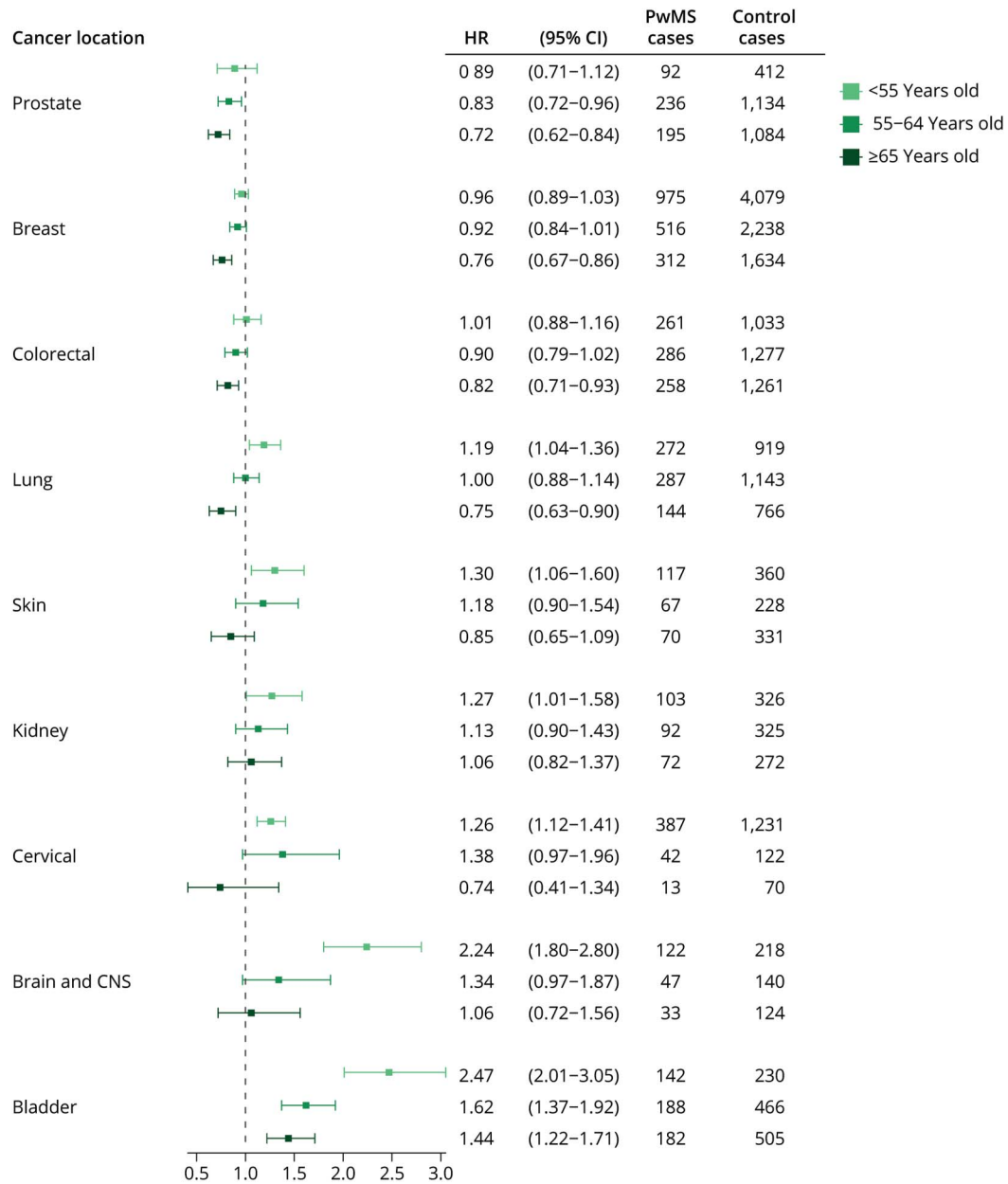
Cancer Mortality Rates

Crude cancer mortality rates were 2,381 per 100,000 PYs (95% CI 2,322–2,441) for controls vs 2,378 (95% CI 2,264–2,497) for PwMS, with an adjusted incidence rate ratio (IRR) of 1.06 (95% CI 1.00–1.12) (MS vs controls; eTable 6). Although not significant, we observed lower rates in PwMS for both brain and CNS (IRR 0.76, 95% CI 0.56–1.02) and kidney (IRR 0.76, 95% CI 0.50–1.09) cancers. Cancer mortality rates were increased in colorectal (IRR 1.28, 95% CI 1.08–1.50) and bladder (IRR 1.53, 95% CI 1.21–1.92) cancer. The remaining cancer types showed no difference.

Discussion

In this 10-year nationwide study that included >140,000 PwMS, MS was associated with a small overall increased cancer risk compared with that in the general population, matched for sex, age, residence, insurance scheme, and period. The risk fluctuated depending on the type of cancer. Although we found a significant increase, our estimates are comparable with other studies^{13,14,18} that did not have sufficient statistical power to detect such a small change. Studies vary greatly regarding population, design, period, and case ascertainment, thus making comparison challenging, and leading to discrepancies in pooled estimates from meta-analyses.^{37–39} Our study estimate is much lower than the one reported by the previous French study that did not match on residence.²³ Regions in the north and northeast of France have higher MS prevalence,⁴⁰ and they also have a higher prevalence of lifestyle-related cancer risk factors, such as smoking and alcohol drinking.^{41,42} This results in a potential overestimation of the cancer risk in PwMS if not adjusted for residence. We used residence at entry as a matching criterion to partially adjust for residual confounders that we could not adjust in our analysis. Moreover, we also had a longer observation period (2012–2021 vs 2008–2015) and a longer preinclusion period to exclude prevalent cancer cases (3 years vs 12 months). We also used a different model for the survival analysis (Fine and Gray vs Cox model), and this could help to explain the difference in estimates between our study and the previously

Figure 5 Results of the Fine and Gray Model to Assess the Risk of Cancer by Cancer Type in PwMS Compared With the General Population Stratified by Age at Entry



HR = hazard ratio; PwMS = people with multiple sclerosis.

published French study.²³ In addition, our cancer case definition, drafted in collaboration with INCa, was less restrictive (1 cancer occurrence vs 2 cancer occurrences). Although a more sensitive case definition could lead to the identification of false positives, we minimized this risk by excluding individuals with a cancer-LTD status but no cancer treatment.

Cancer risk was higher in women than in men. It could be explained by differences in sex-specific cancer, with a high risk of cervical cancer and bladder cancer specifically in women. However, this difference was mostly driven by a risk reduction

by 20% for prostate cancer, which is the most common cancer in men. Indeed, when excluding prostate cancer from our analysis, both men and women estimates became comparable. Moreover, our results showed that age at entry acted as an effect modifier of the cancer risk (overall and by location): the risk was higher in the group younger than 55 years and lower in the group aged 65 years and older. This could be due to differences in screening behaviors because we found lower rates of cancer screening in older PwMS. Lower use of cancer screening, especially in older individuals, could lead to an underestimation of cancer risk in PwMS, especially regarding breast and colorectal cancer.

Table 2 Cancer Screening During the Follow-Up

	PwMS	Controls	Absolute % difference	p Value
Breast cancer				
Patients eligible: women, 50–74	55,126	218,744		
Years of eligibility, mean (SD)	6.6 (3.3)	6.8 (3.3)		
At least 1 mammogram	35,761 (64.9)	156,713 (71.6)	–6.7	<0.001 ^a
At least 1 mammogram, by age				<0.001 ^b
<55	20,152 (68.2)	83,633 (71.8)	–3.6	
55–64	11,627 (65.8)	52,728 (74.6)	–8.8	
65–74	3,982 (50.5)	20,352 (64.4)	–13.9	
Cervical cancer				
Patients eligible: women, 25–64	84,832	339,328		
Years of eligibility, mean (SD)	6.9 (3.3)	7.0 (3.3)		
At least 1 Pap smear, all	51,192 (60.3)	207,949 (61.3)	–1.0	<0.001 ^a
At least 1 Pap smear, by age				<0.001 ^b
<35	14,137 (67.2)	54,206 (64.4)	2.8	
35–44	16,019 (70.0)	62,849 (68.7)	1.3	
45–54	14,821 (60.1)	62,236 (63.0)	–3.0	
55–64	6,215 (38.3)	28,658 (44.1)	–5.8	
At least 1 HPV test, all	17,193 (20.3)	65,591 (19.3)	0.9	<0.001 ^a
At least 1 HPV test, by age				<0.001 ^b
<35	5,711 (27.1)	19,927 (23.7)	3.5	
35–44	6,304 (27.5)	23,571 (25.8)	1.8	
45–54	4,706 (19.1)	19,956 (20.2)	–1.1	
55–64	472 (2.9)	2,137 (3.3)	–0.4	
At least 1 Pap smear or HPV test, all	53,582 (63.2)	217,576 (64.1)	–1.0	<0.001 ^a
At least 1 Pap smear or HPV test, by age				<0.001 ^b
<35	14,858 (70.6)	57,044 (67.8)	2.8	
35–44	16,844 (73.6)	66,328 (72.5)	1.1	
45–54	15,511 (62.9)	64,856 (65.7)	–2.8	
55–64	6,369 (39.2)	29,348 (45.2)	–6.0	
Colorectal cancer				
Patients eligible: men and women, 55–74	78,579	315,592		
Years of eligibility, mean (SD)	6.5 (3.3)	6.7 (3.3)		
At least 1 test, all	27,221 (34.6)	116,557 (36.9)	–2.3	<0.001 ^a
At least 1 test, by age				<0.001 ^b
<55	15,415 (37.0)	62,030 (36.9)	0.1	

Continued

Table 2 Cancer Screening During the Follow-Up (continued)

	PwMS	Controls	Absolute % difference	p Value
55-64	9,134 (35.7)	41,315 (40.3)	-4.6	
65-74	2,672 (23.6)	13,212 (29.2)	-5.5	

Abbreviations: HPV = human papillomavirus; PwMS = people with multiple sclerosis. Eligibility ended at the end of follow-up or when participants reached the age limit. Categorical variables are summarized by count n (%).

^a χ^2 test for proportion comparison.

^b Test for interaction between age and comparison groups.

The location-specific results showed a significant 71% increase in bladder cancer occurrence, concordant with previous findings.^{8,11,14,26} This difference remained significant across all subgroups and was even more pronounced in women. MS can lead to urological complications, resulting in higher prevalence of bladder cancer risk factors, such as chronic urinary tract infection and indwelling catheterization.^{43,44} Other risk factors, such as long-term use of cyclophosphamide and lifestyle factors, also might have a role. This remains a large increased risk that must be taken into account when providing preventive care to PwMS, and potential causes need to be further investigated.

The risk of cervical cancer was increased in PwMS while most studies reported no difference.⁴⁵ This study had sufficient power to detect this increase, compared to previous studies which included very few cases of cervical cancer (<50). Moreover, a recent study found that the risk of cervical abnormalities increased in women treated with high-efficacy DMTs.⁴⁶ The observed increased risk could be explained by specific risk factors in the French MS population, such as potential higher HPV infection rates. In the group younger than 35 years and 35-44-year group, more PwMS had undergone Pap smear than controls, which might result in earlier diagnosis, surveillance bias, and risk overestimation.

We observed an overall risk reduction by 9% for breast cancer that remained significant only in the group aged 65 years and older. This result should be carefully interpreted because it could be the result of low rates of breast cancer screening in older women with MS. Last, prostate cancer risk was significantly reduced by 20% in PwMS. Although prostate cancer incidence depends largely on screening practices,⁴⁷ there is no population screening program for this tumor in France and we could not adjust for it. A 2021 Canadian study found a decrease in prostate cancer incidence that did not translate to a decreased prostate cancer mortality, further suggesting that this difference might be due to lower detection in PwMS.¹⁴ Although the previous French study found an increase in prostate cancer risk,²³ all other studies found no difference^{7,26} or a decreased risk.^{5,8,9,12,14}

To our knowledge, with 703,245 participants and 40,164 cancer cases over a 10-year observation period, this is the largest study on MS and cancer incidence to date. This allowed us to detect

smaller effect sizes, perform subgroup analyses, and investigate less common tumor types (eTables 7 and 8). Similarly, comparing cancer screening for the 3 national programs of breast, colorectal, and cervical cancer led to a more comprehensive understanding of the role of surveillance bias in our study.

In addition, this study described cancer screening in MS, compared with that in a control group from the general population, and identified gaps in cancer preventive care in PwMS, confirming previously described results of lower rates of Pap test and mammography in MS.⁴⁸ Indeed, according to the concept of competing treatment demands, the high levels of disability and comorbidities in some PwMS are risk factors of low levels of preventive care.⁴⁹ In agreement, the gap in cancer screening between PwMS and controls widened with age, resulting in suboptimal screening practices in our MS population. Another strength of our study lies in the statistical model used. Because death occurs 5 to 10 years earlier in MS compared with that in the general population,⁴ it acts as a competing event that can lead to overestimating the cancer risk in PwMS (i.e., the group with earlier death occurrence); hence, competitive risk analyses such as Fine and Gray models are optimal to minimize this potential bias. Regarding the accuracy of cancer screening indicators, the SNDS database comprises all medical procedures conducted in France (public and private).²⁹ Moreover, for both cervical and colorectal cancer, the procedures identified are specific to screening and not diagnostic testing. Regarding breast cancer, it is possible that some mammography was performed for other reasons than screening purposes; however, we did restrict our observation to women eligible for the national screening program (50-74 years). We also performed a sensitivity analysis stratifying mammography use by breast cancer status that showed similar results (eTable 9). Because French data do not provide information on topics covered during physician visits (no ICD-10 codes or text), to adjust for preventive care use, one must adjust for medical screening procedures specific to each disease. Further studies on preventive care use in MS for cancer types without a national screening program are needed to deepen our understanding of cancer and MS.

This study has some limitations. The SNDS database was not originally constructed for epidemiologic purposes and does

not contain physician diagnoses during outpatient visits, laboratory results, and self-reported disease history. Therefore, algorithms are used to identify different diseases. Administrative health care data sets typically lack important health-related information, and therefore, we could not adjust our analyses for education level, income, socioeconomic factors, and individual lifestyle factors (e.g., smoking, alcohol consumption, and sedentary lifestyle) but did match 4:1 on residence to partially control for those behaviors; however, some residual confounding may be left (eTable 6). We could not investigate the effect of clinical characteristics (type of MS, disability level, or cancer stage at diagnosis). Available comorbid diseases associated with cancer, such as cardiovascular diseases, were not included in the analysis because they could be direct consequences of MS and on the causal pathway of the studied relationship, leading to a biased estimate. Finally, because information on DMT use was only available from 2009 onward and DMT prescription is highly dependent on the type of MS, disability level, and health status of the patient, we could not adjust for long-term exposure to immune modulators.⁵⁰

Although both case definitions for MS and cancer were established in collaboration with experts and adapted from validated algorithms,^{2,31,33} their exact validity has yet to be determined; hence, there is still potential for misclassification due to the absence of validation by a clinician or use of registry. It is possible that PwMS with no MS-LTD status, no MS hospitalization, and no MS-specific DMT reimbursement for the observation period of 12 years were missed. However, with the long study period duration, we hypothesize that the number of PwMS missed is very low and unlikely to affect our estimates. Similarly, we might have missed more noninvasive cancers that only required treatment with drugs not specific to cancer or untreated cancers. Some recurrent cancer cases may have been identified as the first incident cancer in the absence of cancer-LTD status declared and with no cancer-related health care use in the previous 3 years. PwMS use health care services more often and frequently than the general population, leading to a potential surveillance bias in cancer diagnosis and treatment. This could have led to a better identification of recurrent cancer cases before inclusion and earlier identification of incident cases and consequently to an overestimation of the cancer risk in MS. This issue is particularly relevant for the observed 68% risk increase in brain and CNS cancers. This increase, although concordant with previous studies,^{7,8,12,26} is most likely due to surveillance bias because PwMS undergo brain magnetic resonance imaging much more frequently than the general population, resulting in earlier diagnosis and treatment of brain tumors. This is further suggested by the 24% decrease in cancer mortality rates in MS for this cancer type (eTable 10).

Cancer incidence was increased in PwMS compared with the general population but varied greatly depending on cancer type, age, and sex. Cancer incidence differences depended largely on age, with an increased risk in the group younger

than 55 years and a risk decrease in the group aged 65 years and older. This difference could be explained by an ascertainment bias that fluctuates with age or might be due to our study design. There was a very large increase in the incidence of bladder cancer in both sexes and all age subgroups. The incidence of cervical and kidney cancer was also increased, but not that of lung cancer. The incidence of prostate, breast, and colorectal cancer was decreased, partially because of lower cancer screening in the older MS age groups. More research is needed, specifically on the role played by ascertainment bias and screening adherence in the observed increased cancer risk in PwMS.

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Appendix Authors

Name	Location	Contribution
Chloe Pierret, MSc	Rennes University, EHESP, CNRS, Inserm, ARENES UMR 6051, RSMS U 1309, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
Aurelien Mulliez, MSc	Clermont-Ferrand University Hospital Center, France	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Christine Le Bihan-Benjamin, MD, PhD	Survey, Data Science and Assessment Division, French National Cancer Institute-InCA, Boulogne-Billancourt, France	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Xavier Moisset, MD, PhD	Clermont-Ferrand University Hospital Center; Clermont Auvergne University, NeuroDol U1107, Clermont-Ferrand, France	Drafting/revision of the manuscript for content, including medical writing for content

Continued

Appendix (continued)

Name	Location	Contribution
Philippe-Jean Bousquet, MD, PhD	Survey, Data Science and Assessment Division, French National Cancer Institute-InCA, Boulogne-Billancourt, France	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
Emmanuelle Leray, PhD	Rennes University, EHESP, CNRS, Inserm, ARENES UMR 6051, RSMS U 1309, France	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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