

# Incidence of malignancy in multiple sclerosis: A cohort study in the Danish Multiple Sclerosis Registry

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Multiple Sclerosis Journal—  
Experimental, Translational  
and Clinical

October-December 2021,  
1–10

DOI: 10.1177/  
20552173211053939

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## Abstract

**Background:** The association between multiple sclerosis and malignancy is controversial and a current appraisal is needed.

**Objective:** To determine the incidence of malignancy in patients with multiple sclerosis compared with the general population and in relation to disease-modifying therapy.

**Methods:** Patients with multiple sclerosis (1995–2015) were matched by birth year and sex to individuals without multiple sclerosis in the general population. Patients with multiple sclerosis initiating disease-modifying therapy were evaluated using landmark period analysis. Malignancy risk was assessed by incidence rates, incidence rate ratios, and standardised incidence ratios.

**Results:** The standardised incidence ratio of any malignancy (excluding non-melanoma skin cancer) in patients with multiple sclerosis ( $n = 10,557$ ) was 0.96 (95% CI 0.88–1.06), and there was no increased incidence of specific malignancy types compared with the general population cohort ( $n = 103,761$ ). At the 48-month landmark period, the age-adjusted incidence per 100,000 person-years of any malignancy (excluding non-melanoma skin cancer) was 436.7 (95% CI 361.0–512.4) in patients newly treated with immunomodulator-only and 675.1 (95% CI 130.4–1219.9) in patients newly treated with immunosuppressant-only.

**Conclusions:** There was no increased incidence of malignancy overall or by type in patients with multiple sclerosis compared neither with the general population nor in relation to disease-modifying therapy.

**Keywords:** Multiple sclerosis, malignancy, Denmark, cohort, registry, incidence, disease-modifying therapy

## Introduction

The association between multiple sclerosis (MS) and malignancy is controversial. Persistent inflammation or chronic immunosuppression may promote tumour generation, while the action of activated inflammatory cells in MS may decrease tumour growth, promoting immunosurveillance.<sup>1</sup> Correspondingly, studies of the association between MS and malignancy have produced conflicting results.<sup>2–14</sup>

The introduction of disease-modifying therapy (DMT) in the mid-1990s reformed the treatment of MS. Currently, DMT is used to reduce MS relapses by modulating and/or suppressing the immune

system.<sup>15</sup> DMT can be categorised according to the mechanism of action as an immunomodulator (IM) or immunosuppressant (IS).<sup>16</sup> Due to their mechanisms of action, IM and IS have been postulated to modulate the risk of malignancy.<sup>17,18</sup> There is, however, currently no strong evidence in the literature for an augmented risk of malignancy in patients with MS receiving IM, and data on IS are scarce.

Given the introduction of DMT to conventional MS treatment, it is relevant to examine the incidence of malignancy overall and by type in a large and recent Danish cohort of patients with MS. The objective of this study is to present a current account of the

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incidence and risk of any malignancy, and malignancy by type in patients with MS compared with the general population and in relation to their use of DMT.

## Methods

### Data sources

This nationwide, population-based cohort study used linked data from the Danish Multiple Sclerosis Registry (DMSR), the Danish Cancer Registry (DCR) and the Danish National Patient Registry (DNPR). All Danish residents are assigned a unique personal identifier by the Danish Civil Registration System which allows linkage between medical registries.<sup>19</sup>

The DMSR was used to identify MS diagnoses. The DMSR receives information from all Danish neurology departments managing the diagnosis and treatment of MS. Since 1996, it has been mandatory to notify the registry with clinical follow-up data for all patients receiving DMT. The completeness of the registry is estimated to be approximate 90%.<sup>20</sup>

The DCR was used to identify malignancy.<sup>21</sup> Data recorded for each individual include the cancer stage and the date of diagnosis. Reporting a cancer event is mandatory, and the completeness of the registry is close to 100%.<sup>22,23</sup>

The DNPR, including data from all hospital admissions, was used to define baseline comorbidities.<sup>24</sup> Discharge diagnoses regarding patients using public hospital services have been included since 1995 (including specialist outpatient and emergency visits) and private hospital services since 2003.<sup>25</sup>

The study was conducted in accordance with Danish laws protecting personal data use for research purposes. The study protocol was approved by the Danish Data Protection Agency. According to Danish legislation, no ethical approval is needed for purely registry-based studies.

### Study population and cohort definition

This analysis compared data from three cohorts, termed the MS cohort, the general population cohort, and the newly treated cohort.

The MS cohort encompassed patients given a definite MS diagnosis between 1 January 1995 and 31 December 2015. The index date was the 1 January of the year of the MS diagnosis. The cohort included

patients older than 18 years at the index date and with  $\geq 12$  months of patient history prior to the index date. Patients with a prior diagnosis of any invasive malignancy were excluded.

For the general population cohort, we matched each patient with MS on exact birth year and sex with up to 10 individuals without MS and prior invasive malignancy. The index date for individuals without MS was identical to that of their matched patient with MS.

The newly treated cohort included treatment-naïve patients with MS, treated for the first time with one DMT of interest between 1995 and 2016. The index date was defined as the date of initiation with a DMT.

All three cohorts were followed until the first malignancy diagnosis, death, emigration or the end of the study period (31 December 2016), whichever came first.

### Outcomes

The study outcome was a first-time malignancy diagnosis in the DCR (see Supplemental Table S1 for code lists). We conducted the analyses both including and excluding non-melanoma skin cancer (NMSC). In analyses excluding NMSC, NMSC was not recorded as an event and follow-up continued. The exclusion of NMSC allowed other malignancies to be analysed without being masked by NMSC. Malignancies by type were categorised following the GLOBOCAN 2018 classification.<sup>26</sup> In DCR, the stage was classified as localized, regional or distant spread until 2004. Thereafter, the stage of solid tumours has been classified according to the TNM system. For solid tumours, we categorized stages as localized, regional spread, distant spread and missing.

Due to data privacy considerations, only malignancy types with  $\geq 5$  events were displayed.

### Exposure

The DMTs included in this analysis were captured in the DMSR and categorised as either IM or IS. IM treatments included interferon (IFN)  $\beta$ -1a, IFN  $\beta$ -1b, glatiramer acetate and pegylated IFN  $\beta$ -1a. IS treatments included teriflunomide, fingolimod, dimethyl fumarate, mitoxantrone, natalizumab, methotrexate and rituximab.

We defined exposure at the start of DMT (=landmark 0) as the DMT prescribed at the index date of the

newly treated cohort, regardless of subsequent changes.

For the landmark period analysis, we additionally categorised exposure to DMT during follow-up at three different time points, that is, at 12, 24 and 48 months after the start of follow-up. Patients were categorised into exposure to IM-only and IS-only based on the treatment they received in the defined landmark period, regardless of treatment changes after the landmark period. Patients who discontinued their treatment (defined as a gap in treatment longer than 90 days), switched from IM to IS treatment or vice versa, presented with a malignancy diagnosis, or were lost to follow-up before the time point of the landmark were not included in the analysis of the specific landmark period (Supplemental Figure S1). As a sensitivity analysis, patients who received both IM and IS treatment during the 48 months landmark period were included as a separate exposure group.

#### *Covariates*

The baseline comorbidities were chosen based on knowledge from the existing literature regarding the risk of malignancy in patients with MS and included: diabetes mellitus, autoimmune diseases, chronic obstructive pulmonary disease (COPD) and alcohol abuse. These were identified based on diagnoses recorded before the index date in the DNPR.

#### *Statistical analysis*

First, descriptively, we estimated incidence rates (IRs) of any malignancy and malignancy by type in the MS cohort.

Secondly, as a comparison with the general population, we calculated SIRs as the ratio of the observed number of malignancies in the MS cohort, and the number of malignancies that would be expected in a general population with a similar distribution of age, sex and calendar period. The expected number of malignancies was estimated based on malignancy IRs derived from the entire Danish population across 5-year age groups, sex and 5-year calendar periods and multiplied by the number of PY of the MS cohort. SIRs were stratified by sex and presented with 95% confidence intervals (CIs).

Thirdly, we compared the incidence of malignancy by type and by stage (restricted to solid tumours only) in the MS and general population cohorts, computing unadjusted incidence rate ratios (IRRs) with 95% CIs. We adjusted the IRRs for the calendar period at MS diagnosis, age, sex and comorbidity in an exact

Poisson regression model with the matching dissolved.

Finally, the association between time-dependent DMT exposure and malignancies was assessed. To avoid reverse causation, that is, those symptoms of cancer lead to changes in treatment and to acknowledge the typically long period of cancer development and latency of any carcinogenic or anti-neoplastic drug effects,<sup>27</sup> we started follow-up at four different landmarks. Treatment patterns for patients with MS in the newly treated cohort were categorised from the time of DMT initiation until the specific landmark (baseline and 12, 24 and 48 months), and follow-up for cancer then started at the date of the specific landmark (Supplemental Figure S1).

Age-adjusted IRs were calculated using the weighted average of the unadjusted IRs specific to each age group and were stratified by sex. We calculated the proportion of patients with MS in each specific age group and weights were based on the distribution of ages in the newly treated cohort. Patients who received both IM and IS treatment were only analysed at the 48 months landmark.

#### *Data availability statement*

In Denmark, registry data are kept at secured research servers at either Statistics Denmark or at the Danish Health Data Authority. Data sharing is not permitted according to Danish legislation.

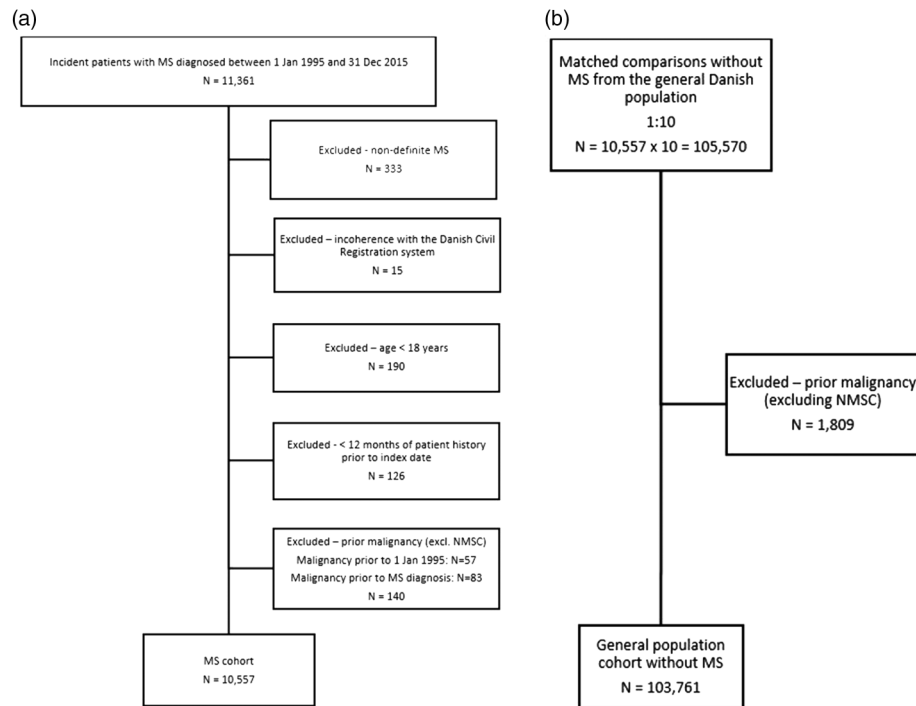
## **Results**

#### *Patient selection*

A total of 10,557 patients were included in the MS cohort (Figure 1A) and matched to 103,761 individuals without MS from the general population (Figure 1B). From the MS cohort, 140 patients were excluded and from the general population cohort 1809 individuals were excluded because of prior malignancy (excl. NMSC) recorded before their MS diagnosis. A total of 8070 patients were included in the newly-treated cohort (Figure 1C).

#### *Patient characteristics*

There were 67.5% women in the MS cohort, with a median age of 39 years (Table 1). The distribution of comorbidities was similar in the MS cohort and the general population cohort. Type of MS was unknown for 34.2% of patients in the MS cohort, and among patients with an identified type of MS, the majority had relapsing-remitting MS (57.4%),



**Figure 1.** Patient selection in the (A) MS cohort, (B) general population cohort and (C) newly-treated cohort  
DMT: disease-modifying therapy; IM: immunomodulator; IS: immunosuppressant; MS: multiple sclerosis; NMSC: non-melanoma skin cancer.

followed by secondary progressive MS (6.5%) and primary progressive MS (1.9%).

In the newly treated cohort, patients receiving IS-only were older (median age 41 years) compared with patients receiving IM-only (median age 38 years). Across landmark periods, the median follow-up was 7–9 years in the IM-only group and 1–5 years in the IS-only group (Figure 2).

#### *Incidence and risk – Any malignancy in the MS cohort*

During a median follow-up of 10 years, the IR of malignancy in the MS cohort was 407.6 (95% CI 370.6–444.5) per 100,000 PY excluding NMSC and 560.6 (95% CI 517.1–604.1) per 100,000 PY including NMSC (Figure 3). The SIRs did not show an increased risk of malignancy compared with the entire Danish population (excluding NMSC, 0.96 [95% CI 0.88–1.06] and including NMSC, 0.98 [95% CI 0.91–1.06]; Figure 3). When stratified by sex, the SIRs showed consistent results (women excluding NMSC, 0.98 [95% CI 0.87–1.09] and including NMSC, 1.02 [95% CI 0.93–1.11]; men excluding NMSC, 0.94 [95% CI 0.79–1.10] and including NMSC, 0.91 [95% CI 0.78–1.05]; Figure 3).

Restricted to solid tumours, the IR per 100,000 PY in the MS cohort was highest for localized stage 319.6 (95% CI 286.7–352.5) decreasing to 80.1 (95% CI 63.65–96.58) for regional spread and 67.8 (95% CI 52.7–82.9) for distant spread. The IR for solid tumours with the unknown stage was 61.63 (95% CI 47.19–76.06). Compared with the general population cohort the adjusted IRRs were 0.93 (95% CI 0.73–1.18) for localized stage, 0.79 (95% CI 0.50–1.25) for regional spread, 0.92 (95% CI 0.42–2.00) for distant spread and 1.10 (95% CI 0.73–1.67) for the unknown stage.

#### *Incidence and risk – Malignancy by type in the MS cohort*

When considering malignancy by type, similarly, no substantial differences in incidence were observed when comparing the MS cohort with the general population cohort (Figure 4). In the MS cohort, the malignancy types with the highest IRs per 100,000 PY were breast cancer (151.7 [95% CI 124.2–179.2]), prostate cancer (95.4 [95% CI 63.8–127.0]) and malignant melanoma (50.1 [95% CI 37.1–63.1]) (Figure 4). For these malignancy types, the adjusted IRRs were 0.91 (95% CI 0.58–1.43), 1.03 (95% CI 0.71–1.49) and 1.43 (95% CI 0.59–

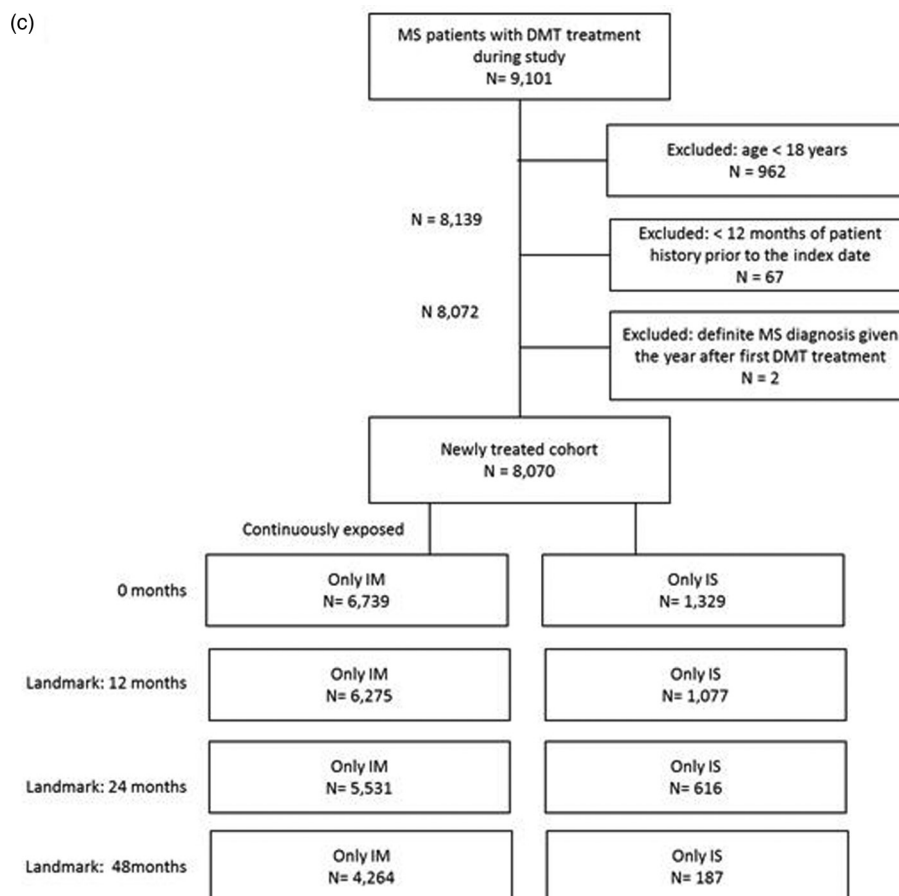


Figure 1. Continued

3.48), respectively. The adjusted IRR for bladder cancer was 1.39 (95% CI 0.57–3.39) (Figure 4).

#### *Incidence of any malignancy in patients with MS newly treated with DMT*

Overall, the incidence of any malignancy (excluding NMSC) in the newly treated cohort of patients with MS was similar in patients receiving either IM-only or IS-only treatment (Figure 2). In the IM-only group, the age-adjusted IRs of any malignancy (excluding NMSC) ranged from 345.6 (95% CI 298.8–392.3) per 100,000 PY at 0 months to 436.7 (95% CI 361.0–512.4) at the 48-month landmark period (Figure 2). The age-adjusted IRs per 100,000 PY in the IS-only group ranged from 414.1 (95% CI 182.5–645.6) at 0 months to 675.1 (95% CI 130.4–1219.9) at the 48-month landmark period.

For 936 patients, who at the 48-month landmark had received both IM and IS treatment, the age-adjusted IR per 100,000 PY for any cancer (excluding NMSC) was 325.3 (95% CI 112.0–538.7).

When including NMSC in the analysis of the incidence of any malignancy in patients with MS newly treated with DMT, at the 48-month landmark period, the age-adjusted IR was 611.7 (95% CI 521.1–702.3) in the IM-only group (data not shown). In the IS-only group, the age-adjusted IR at the 48-month landmark period was 922.6 (95% CI 277.5–1567.7) including NMSC (data not shown).

#### **Discussion**

In this nationwide, population-based Danish study, we did not observe an increased incidence of any malignancy and malignancy by type in patients with MS compared with the general population.

Our results are generally consistent with most previous studies that did not support a different risk of malignancy in patients with MS compared with the general population.<sup>2–4,8,9,13</sup> In contrast, three previous studies reported higher overall incidences of malignancy in patients with MS generally based on prominently increased risks of specific malignancy types,

**Table 1.** Characteristics of patients in the MS cohort, the general population cohort, and the newly-treated cohort.

	MS cohort <sup>a</sup>	General population cohort <sup>a</sup>	Newly-treated cohort <sup>b,c</sup>	
			IM-only N = 6739	IS-only N = 1329
Female, <i>n</i> (%)	7128 (67.5)	69,906 (67.4)	4720 (70.0)	851 (64.0)
Age in years, median (IQR)	39 (31–48)	39 (31–48)	38 (31–45)	41 (32–49)
Year of MS diagnosis, <i>n</i> (%)				
1995–2004	4804 (45.5)	–	2999 (44.5)	172 (12.9)
2005–2015	5753 (54.5)	–	3740 (55.5)	1157 (87.1)
Type of MS, <i>n</i> (%)				
Relapsing-remitting	6055 (57.4)	–	5555 (82.4)	690 (51.9)
Primary progressive	200 (1.9)	–	<5 (0.0)	9 (0.7)
Secondary progressive	689 (6.5)	–	614 (9.1)	47 (3.5)
Unknown/missing	3613 (34.2)	–	568 (8.4)	583 (43.9)
Time from MS diagnosis to first DMT in years, mean	2	–	2	1
Comorbidities, <i>n</i> (%)				
Diabetes mellitus	161 (1.5)	1365 (1.3)	115 (1.7)	23 (1.7)
Autoimmune diseases	211 (2.0)	1827 (1.8)	152 (2.3)	30 (2.3)
COPD	57 (0.5)	538 (0.5)	36 (0.5)	9 (0.7)
Alcohol abuse	293 (2.8)	2910 (2.8)	173 (2.6)	53 (4.0)
Duration of follow-up in years, median (IQR)	10 (6–15)	10 (6–15)	9 (5–13)	2 (1–3)

COPD: chronic obstructive pulmonary disease; DMT: disease-modifying therapy; IM: immunomodulator; IQR: interquartile range; IS: immunosuppressant; MS: multiple sclerosis.

<sup>a</sup>Index date = date of definite MS diagnosis (in matched patients with MS).

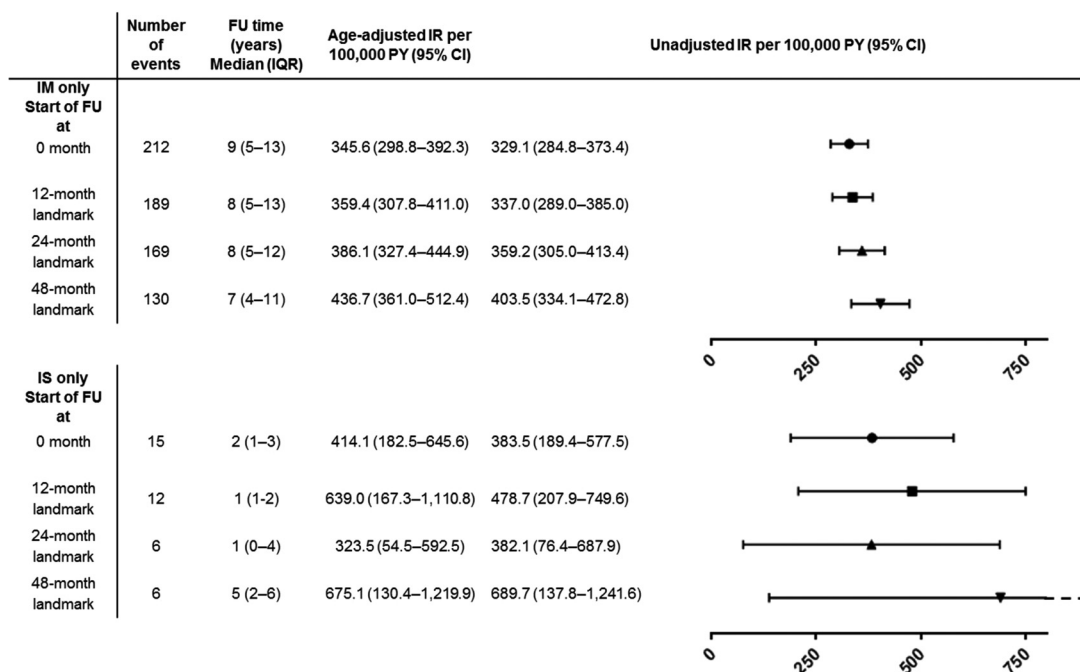
<sup>b</sup>Index date = date of DMT initiation.

<sup>c</sup>At 0 months.

which may have skewed the overall findings.<sup>6,11,28</sup> Data from the National Health Insurance System of Taiwan suggested a greater risk of any malignancy in patients with MS (hazard ratio [HR] 1.85 [95% CI 1.26–2.74]), which was likely driven by an increased risk of breast cancer (HR 2.23 [95% CI 1.11–4.46]).<sup>11</sup>

Additional to breast cancer, other malignancy types including NMSC, urinary tract tumours, and respiratory organ cancer have been suggested to have a higher incidence in patients with MS.<sup>6,28</sup> In our study, patients with MS had a nearly 40% increased risk of bladder cancer compared with the general population cohort, however, this estimate was based on low numbers, had low statistical precision, and might be explained by detection bias. Neurogenic bladder symptoms may incline patients with MS to consult a urologist leading to a higher detection rate

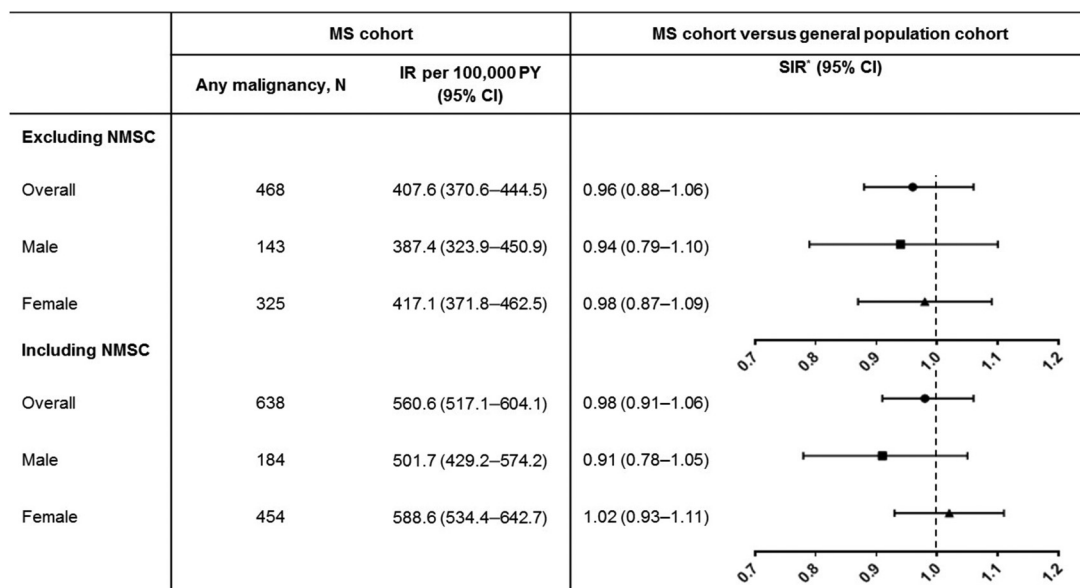
of malignancies in the urinary tract. An increased incidence of brain tumours in patients with MS has also been suggested in previous studies, but this may also be influenced by detection bias arising from the use of magnetic resonance imaging to analyse the natural disease history of MS and was not observed in our study.<sup>6,28,29</sup> Another finding in our study was a 40% higher IR for malignant melanoma in the MS cohort compared with the general population cohort, which was observed across treatments. However, the statistical precision was low and prohibited any firm conclusion. A literature review of non-interventional studies by Marrie et al.<sup>13</sup> in 2015, did not identify an increased risk of malignant melanoma in MS. A previously published study of cancer incidence in Danish patients with MS was conducted over the same time period and did show an increased risk of malignant melanoma (SIR 1.51 [95% CI 1.13–1.98]).<sup>8</sup> In that study, the DCR and the DNPR were



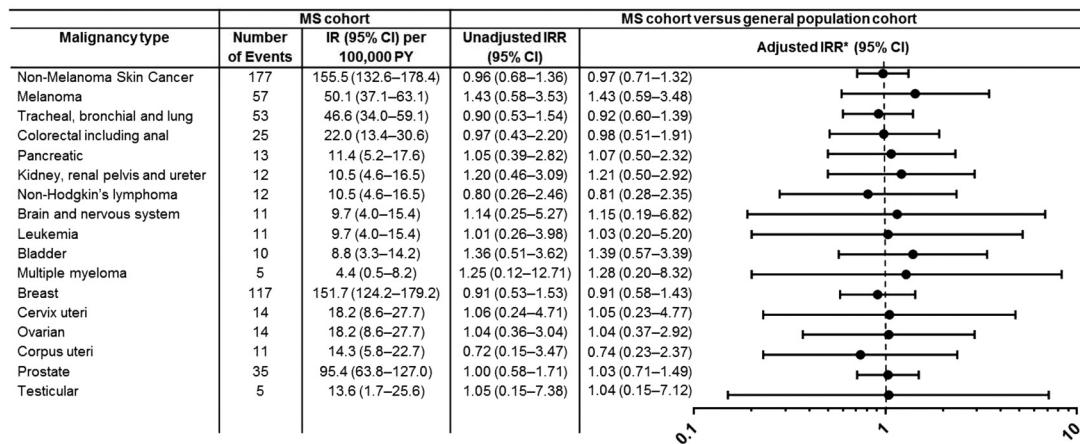
**Figure 2.** Unadjusted and age-adjusted incidence rate of any malignancy in the newly-treated cohort (excluding NMSC) CI: confidence interval; FU: follow-up; IM: immunomodulator; IQR: interquartile range; IS: immunosuppressant; NMSC: non-melanoma skin cancer; PY: person-years.

also linked, however, the conflicting results might be explained by other methodological differences. Whereas the previous study applied a population-level approach and SIRs were generated using national cancer statistics for the Danish population,

we used a patient-level approach with the matching of patients with MS to individuals without MS. Furthermore, we adjusted on predominantly validated comorbidities,<sup>25</sup> while the previous study adjusted only for age, sex and calendar year.<sup>8</sup>



**Figure 3.** Incidence rate of any malignancy in the MS cohort compared with the general population cohort \*SIRs were stratified by sex. CI: confidence interval; IR: incidence rate; MS: multiple sclerosis; NMSC: non-melanoma skin cancer; PY: person-years; SIR: standardised incidence ratio.



**Figure 4.** Incidence of malignancy by type in the MS cohort compared with the general population cohort  
 \*Adjusted for calendar period at MS diagnosis, age, sex and comorbidity (diabetes mellitus, autoimmune diseases, COPD, alcohol abuse).  
 CI: confidence interval; COPD: chronic obstructive pulmonary disease; IR: incidence rate; IRR: incidence rate ratio; PY: person-years.

Conversely, several previous studies have suggested a decreased risk of malignancy in patients with MS.<sup>3,14,18,29–31</sup> In a recent meta-analysis of five pooled studies, it was observed that the risk of cancer in patients with MS was less than that in the general population with a pooled relative risk of 0.83 (95% CI 0.73–0.96).<sup>14</sup> Lebrun et al. reported overall malignancy SIRs as low as 0.29 (95% CI 0.17–0.45) in men with MS and 0.53 (95% CI 0.42–0.66) in women with MS; however, the data used for patients with MS assessed in the study were from registries which were less complete.<sup>18</sup>

Our findings of largely similar incidences of any malignancy (excluding NMSC) in patients with MS receiving IM-only and IS-only treatments are coherent with the majority of relevant non-interventional studies.<sup>3,31–33</sup> For example, in a nested case-control study linking 5146 patients from the British Columbia MS database to the Cancer Registry, there was no evidence that longer IFN $\beta$  exposure increased the risk of malignancy over a 12-year follow-up.<sup>31</sup> Although, one study evaluating cancer risk in the same population of patients with MS from British Columbia suggested an increased risk of breast cancer in IFN $\beta$ -treated patients (odds ratio 1.77 [95% CI 0.92–3.42]).<sup>34</sup> A study assessing patients included in the New York State MS Consortium registry did not show a higher risk of cancer after DMT initiation, suggesting a potentially protective effect against cancer by the immune system activation seen in MS.<sup>3</sup> Conversely, two other studies did suggest an increased risk of malignancy following

IS initiation, increasing with longer exposure times.<sup>9,33</sup>

Strengths of the present study include the nationwide design, allowing the inclusion of a large number of patients with MS, and the quality and completeness of the DMSR and the DCR.<sup>20–22</sup> Further, all DMT for MS in Denmark is government-financed and free of charge for patients, and regular notification of the DMSR during clinical visits is mandatory. Additionally, using a landmark period analysis allowed us to conduct an intention-to-treat analysis while adjusting for baseline variables.

Limitations include that ‘any malignancy’ was considered as a single outcome in the MS cohort analyses regardless of differences in aetiology and pathogenesis of different malignancy types. Denmark currently has three nationwide cancer screening programs. Screening for cervical cancer was implemented in the 1960s, mammography screening for breast cancer in 2009, and screening for colorectal cancer (faecal occult blood test) was implemented in 2014. However, we do not know whether patients with MS have similar participation rates in these programs as the general population. Whilst, overall, we found no increase or decrease in the incidence of any type of malignancy, it is necessary to consider that this could be due to low numbers, as some types of malignancy are rare. Regarding the comorbidities used for adjustment, conditions such as diabetes mellitus may be treated by a general practitioner and thus not completely registered in the DNPR (although



these may be captured in outpatient visits at hospital).<sup>25</sup> Additionally, IM and IS were considered as two homogeneous DMT groups, although, the risk of malignancy might vary across specific IM and IS treatments. Considering the shorter median follow-up in the IS-only group compared with the IM-only group and the latency between DMT exposure and malignancy diagnosis, the IRs calculated for the IS-only group were less precise than for the IM-only group and should be interpreted with caution. Finally, the landmark period analysis incurred a smaller sample size because of the analysis by a series of exposure periods with different selection mechanisms.<sup>35</sup> Lengths of landmark periods were chosen based on consideration of the fact that a longer landmark period may exclude patients from the analysis, thereby limiting statistical power, and a shorter landmark period may provide an incomplete picture of treatment effects.<sup>36</sup>

The present study suggested no excess risk of malignancy in Danish patients with MS compared with the general population. After considering varied exposure to IM or IS, the incidence rates did not suggest any substantial difference in the risk of malignancy but had limited statistical precision.

### Acknowledgements

Medical writing assistance was provided by Farah Johnson-May and Ella Palmer of inScience Communications, Springer Healthcare Ltd, UK, and was funded by Merck Healthcare KGaA, Darmstadt, Germany.

### Declaration of conflicting interests


MN, KV and LSS are salaried employees of Aarhus University/Aarhus University Hospital. The study was partially funded by the healthcare business of Merck KGaA, Darmstadt, Germany as a research grant given to and administered by Aarhus University, Denmark. CF, EB and MS are full-time employees of the healthcare business of Merck KGaA, Darmstadt, Germany. FS has served on scientific advisory boards, been on the steering committees of clinical trials, served as a consultant, received support for congress participation, received speaker honoraria, or received research support for his laboratory from Biogen, the healthcare business of Merck KGaA (Darmstadt, Germany), Novartis, Roche, Sanofi-Genzyme and Teva. MM has served on the scientific advisory board for AbbVie, Alexion, Biogen, the healthcare business of Merck KGaA (Darmstadt, Germany), Novartis, Roche and Sanofi, and has received honoraria for lecturing from Biogen, the healthcare business of Merck KGaA (Darmstadt, Germany), Novartis and Sanofi, and has received support for congress participation from Biogen,

Genzyme, the healthcare business of Merck KGaA (Darmstadt, Germany) and Roche.

### Funding

The current analysis administered by Aarhus University was partly funded by a research agreement from the healthcare business of Merck KGaA, Darmstadt, Germany (CrossRef Funder ID: 10.13039/100009945). Merck contributed to the design and the protocol of the study but the academic authors made the final determination on which analyses to present and how best to interpret them.

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### Supplemental material

Supplemental material for this article is available online.

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