Cancer Risk for Fingolimod, Natalizumab, and Rituximab in Multiple Sclerosis Patients

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Objective: Novel, highly effective disease-modifying therapies have revolutionized multiple sclerosis (MS) care. However, evidence from large comparative studies on important safety outcomes, such as cancer, is still lacking.
Methods: In this nationwide register-based cohort study, we linked data from the Swedish MS register to the Swedish Cancer Register and other national health care and census registers. We included 4,187 first-ever initiations of rituximab, 1,620 of fingolimod, and 1,670 of natalizumab in 6,136 MS patients matched for age, sex, and location to 37,801 non-MS general population subjects. Primary outcome was time to first invasive cancer.
Results: We identified 78 invasive cancers among treated patients: rituximab 33 (incidence rate [IR] per 10,000 person-years = 34.4, 95% confidence interval [CI] = 23.7–48.3), fingolimod 28 (IR = 44.0, 95% CI = 29.2–63.5), and natalizumab 17 (IR = 26.0, 95% CI = 15.1–41.6). The general population IR was 31.0 (95% CI = 27.8–34.4). Adjusting for baseline characteristics, we found no difference in risk of invasive cancer between rituximab, natalizumab, and the general population but a possibly higher risk with fingolimod compared to the general population (hazard ratio [HR] = 1.53, 95% CI = 0.98–2.38) and rituximab (HR = 1.68, 95% CI = 1.00–2.84).
Interpretation: In this first large comparative study of 3 highly effective MS disease-modifying therapies, no increased risk of invasive cancer was seen with rituximab and natalizumab, compared to the general population. However, there was a borderline-significant increased risk with fingolimod, compared to both the general population and rituximab. It was not possible to attribute this increased risk to any specific type of cancer, and further studies are warranted to validate these findings.

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Multiple sclerosis (MS) usually presents as a relapsing–remitting disease, but over time, in parallel with accumulation of more severe neurological disabilities, most patients convert to a secondary progressive disease course (SPMS).[1] In a minority of patients, the disease is progressive from onset (primary progressive MS [PPMS]).[1]

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The first disease-modifying therapies (DMTs) for MS, interferon-beta and glatiramer acetate, were introduced more than 2 decades ago. Although their effectiveness for protecting against relapses and accrual of neurological disability is relatively modest, they are considered to have beneficial safety profiles, even with long-term exposure. Since then, several additional therapies have been introduced, many of which are considered highly effective therapeutic options.[2] Currently in Sweden, fingolimod, natalizumab, and rituximab are the most frequently used DMTs for therapeutic escalation or initial treatment of more aggressive disease.[3] Natalizumab, approved in 2006, is a monoclonal antibody blocking VLA4 and thereby inhibiting transmigration of lymphocytes across the blood–brain barrier.[4,5] Fingolimod, approved in 2011, is an oral sphingosine-1-phosphate receptor inhibitor that sequesters lymphocytes in lymph nodes, leading to a marked systemic lymphopenia.[6,7] Rituximab, approved for treatment of rheumatoid arthritis (RA) and lymphatic cancers, is a chimeric, B-cell-depleting, anti-CD20 antibody that has been increasingly used off-label in MS after the promising results of 2 phase II trials[8,9] and subsequent observational studies.[10,11] It has now become the most frequently used DMT for MS in Sweden.[3]

Accumulating real-world evidence now supports the notion of a superior effect of newer DMTs in protecting against disability and conversion to SPMS.[12,13] However, despite the widespread use of these newer highly effective DMTs, evidence from large comparative studies on important safety outcomes, such as cancer, is still lacking. Considering the impact of these therapies on immune competence,[14,15] such studies are highly warranted. Randomized controlled trials have limited ability to detect rare safety outcomes due to small cohort sizes and short study durations and have known limitations in the generalizability to real-world patient populations. In contrast, the nationwide Swedish MS register and Sweden's health care and census registers are well suited for investigating safety outcomes in the MS setting and allow for monitoring of rare events without attrition in clinically relevant patient populations. Using the prospectively collected data from these registers, we compared the risk of cancer in a large population of MS patients treated with rituximab, fingolimod, or natalizumab.

Patients and Methods

We performed a nationwide register-based cohort study of rituximab, fingolimod, and natalizumab therapy episodes started between 2011 and (including) 2017 in persons with MS matched to non-MS general population subjects using data from the Swedish MS register linked to the Swedish Cancer Register and other national health care and census registers. This study is part of the larger project Rituximab in Multiple Sclerosis: A Comparative Study on Effectiveness, Safety, and Patient Reported Outcomes, which is funded by a grant from the Patient-Centered Outcomes Research Institute (PCORI) and also includes a large observational drug trial (clinicaltrials.gov: NCT03193866; https://clinicaltrials.gov/ct2/show/NCT03193866). This study was approved by the Regional Ethical Board of Stockholm (reference number: 2017/700-31/4).

Data Sources

The nationwide Swedish MS register, started in 2000, captures longitudinal information on treatments and disease progression among Swedish MS patients.[3] Despite participation being voluntary, it has a reported coverage of more than 80%,[16] and the validity of therapy data is high.[17] The national cancer register, maintained by the National Board of Health and Welfare, contains information on cancer location and morphology, with virtually no missing data.[18] Since 2004, basal-cell carcinomas have also been registered. Other registers used were the national patient register with data on all in- and outpatient visits and the associated diagnosis codes (with high validity);[19] the national prescribed drug register with complete data on all medications collected from pharmacies;[20] national demographic registers with data on age, sex, education, and birth region for all residents; and national registers with data on sick leave and disability pension.

Exposure Definition

We included all first initiations of rituximab, fingolimod, and natalizumab between January 1, 2011, and December 31, 2017, for every patient in the MS register. We used an ever-treated approach, meaning that a started therapy was considered an exposure until an outcome or censoring event, even if the therapy itself had ended before this time. Individuals could be included in more than 1 treatment group as they progressed in treatment over time. We excluded therapy episodes started more than 60 days prior to inclusion in the MS register to avoid potential immortal-time bias. Using the national registries, a non-MS general-population cohort was matched to the included therapy episodes (5 to 1) by age, sex, and location in Sweden using risk-set sampling, that is, comparator subjects were sampled among all individuals living in Sweden and who had not developed MS at the time of the index patient's inclusion. Censoring events were emigration, death, exposure to mitoxantrone (due to its link to cancer[21,22]), and if a general population comparator subject became an MS case, whichever happened first.

Outcome Definition

Outcomes were identified in the national cancer register and included time to first invasive cancer, basal-cell

carcinoma, and cervical intraepithelial neoplasia grade 3 (CIN3). Basal-cell carcinoma and CIN3 were chosen because they are relatively common and have been associated with immune suppression and infection with human papillomavirus, respectively. Several prespecified, specific invasive cancers were also assessed: breast cancer, prostate cancer, melanoma, nonmelanoma skin cancer (not including basal-cell carcinoma), and lymphoma. Analyses of CIN3 and breast cancer were restricted to female subjects, and the analysis of prostate cancer was restricted to males. See Supplementary Table S1 for the International Classification of Diseases for Oncology codes used for the identification of the specific cancers. Analyses were performed separately for the different outcomes, focusing on the first diagnosis of the specified cancer. Cancers other than the one analyzed were not considered censoring events.

Potential Confounders

Pretreatment covariates included in the multiple imputation and propensity score models were: age; sex; birth

TABLE 1A. General Baseline Variables After Multiple Imputation, Before and After Weighting

	Crude			Weighted*		
	Rituximab	**Fingolimod**	**Natalizumab**	**Rituximab**	**Fingolimod**	**Natalizumab**
N	4187	1620	1670	—	—	—
Age, years [mean (std)]	42.9 (11.3)	39.2 (9.8)	35.6 (10.4)	40.6 (11.2)	40.7 (11.1)	40.5 (11.4)
Sex, female [n, (%)]	2968 (70.9)	1104 (68.1)	1215 (72.8)	71.0	72.5	71.9
Place of birth, Nordic countries [n, (%)]	3729 (89.1)	1435 (88.6)	1500 (89.8)	89.0	88.7	90.1
Education level, ≤9y [n, (%)]	444 (10.6)	147 (9.0)	204 (12.2)	10.2	9.8	9.7
Education level, 10-12y [n, (%)]	1970 (47.0)	737 (45.5)	760 (45.5)	46.1	46.4	43.1
Education level, >12y [n, (%)]	1773 (42.3)	737 (45.5)	707 (42.3)	43.6	43.7	47.2
Antidepressant use [n, (%)]	1310 (31.3)	466 (28.8)	446 (26.7)	30.0	31.8	31.3
Antidiabetic use [n, (%)]	128 (3.1)	23 (1.4)	46 (2.8)	2.6	2.2	2.5
Antipsychotic use [n, (%)]	111 (2.7)	22 (1.4)	35 (2.1)	2.2	2.3	2.0
Immunosuppressive use [n, (%)]	52 (1.2)	9 (0.6)	12 (0.7)	1.0	1.2	1.2
Glucocorticoid use [n, (%)]	1220 (29.1)	410 (25.3)	382 (22.9)	26.5	26.3	24.2
Arrhythmia [n, (%)]	63 (1.5)	21 (1.3)	15 (0.9)	1.4	1.4	1.0
Major acute cardiovascular event [n, (%)]	52 (1.2)	9 (0.6)	19 (1.1)	1.2	1.0	1.3
Hospital days, 0 days [n, (%)]	1714 (40.9)	463 (28.6)	568 (34.0)	37.5	38.1	39.9
Hospital days, 1-10 days [n, (%)]	1655 (39.5)	860 (53.1)	753 (45.1)	42.9	42.8	42.5
Hospital days, 11+ days [n, (%)]	818 (19.5)	297 (18.3)	349 (20.9)	19.6	19.0	17.5
Disability pension [n, (%)]	1190 (28.4)	344 (21.2)	214 (12.8)	23.8	25.0	22.3
Sick leave [n, (%)]	1233 (29.4)	505 (31.2)	488 (29.2)	29.6	29.4	30.5
Any invasive cancer >5 years [n, (%)]	67 (1.6)	24 (1.5)	20 (1.2)	1.7	1.4	1.3
Any invasive cancer <5 years [n, (%)]	46 (1.1)	16 (1.0)	15 (0.9)	1.0	1.2	1.1

*Number of events is not presented for the weighted pseudo-population and weights were calculated using our most fully adjusted model for the outcome any invasive cancer: age, sex, birth region, education, previous invasive cancer, arrhythmia, major acute cardiovascular event, use of antidepressants, antipsychotics, antidiabetics, glucocorticoids, and immunosuppressives, hospital days, sick leave, disability pension, MS type, disease duration, number of previous therapies, previous interferon, previous glatiramer acetate, EDSS, SDMT, and MSIS-29.

Notes: MS = Multiple Sclerosis; EDSS = Expanded Disability Status Scale; SDMT = Symbol Digit Modalities Test; MSIS-29 = Multiple Sclerosis Impact Scale; std = standard deviation; Definitions of disease and drug use characteristics can be found in Supplemental table S2.

TABLE 1B. Multiple Sclerosis Baseline Variables After Multiple Imputation, Before and After Weighting

	Crude			Weighted*		
	Rituximab	Fingolimod	Natalizumab	Rituximab	Fingolimod	Natalizumab
N	4187	1620	1670	—	—	—
MS type, PPMS [n, (%)]	168 (4.0)	3 (0.2)	8 (0.5)	2.4	1.9	1.3
MS type, PRMS [n, (%)]	71 (1.7)	13 (0.8)	16 (1.0)	1.3	1.3	1.0
MS type, RRMS [n, (%)]	3215 (76.8)	1519 (93.8)	1568 (93.9)	84.1	83.1	83.8
MS type, SPMS [n, (%)]	732 (17.5)	84 (5.2)	77 (4.6)	12.2	13.7	13.8
Disease duration [mean (std)]	10.3 (8.7)	9.0 (6.8)	6.1 (6.4)	9.2 (8.0)	9.4 (7.9)	9.1 (8.0)
Number of previous therapies, 0 [n, (%)]	1032 (24.6)	196 (12.1)	515 (30.8)	23.6	20.8	22.8
Number of previous therapies, 1 [n, (%)]	1657 (39.6)	904 (55.8)	963 (57.7)	46.3	46.8	46.7
Number of previous therapies, 2+ [n, (%)]	1498 (35.8)	520 (32.1)	192 (11.5)	30.1	32.3	30.4
Previous interferon [n, (%)]	2371 (56.6)	1173 (72.4)	975 (58.4)	59.9	60.7	57.8
Previous glatiramer acetate [n, (%)]	697 (16.6)	369 (22.8)	290 (17.4)	18.2	19.1	20.6
EDSS [mean (std)]	2.8 (2.0)	2.2 (1.6)	2.4 (1.6)	2.6 (1.8)	2.6 (1.8)	2.5 (1.8)
SDMT [mean (std)]	50.8 (14.8)	53.6 (14.3)	50.7 (12.9)	51.4 (14.3)	51.5 (13.8)	51.2 (13.3)
MSIS-29 Physical [mean (std)]	2.2 (1.0)	1.9 (0.9)	2.1 (0.9)	2.1 (1.0)	2.1 (0.9)	2.0 (0.9)
MSIS-29 Psychological [mean (std)]	2.4 (1.0)	2.2 (1.0)	2.5 (1.0)	2.4 (1.0)	2.4 (1.0)	2.3 (1.0)

*Number of events is not presented for the weighted pseudo-population and weights were calculated using our most fully adjusted model for the outcome any invasive cancer: age, sex, birth region, education, previous invasive cancer, arrhythmia, major acute cardiovascular event, use of antidepressants, antipsychotics, antidiabetics, glucocorticoids, and immunosuppressives, hospital days, sick leave, disability pension, MS type, disease duration, number of previous therapies, previous interferon, previous glatiramer acetate, EDSS, SDMT, and MSIS-29.

Notes: MS = Multiple Sclerosis; PPMS = Primary Progressive MS; PRMS = Progressive-Relapsing MS; RRMS = Relapsing-Remitting MS; SPMS = Secondary Progressive MS; EDSS = Expanded Disability Status Scale; SDMT = Symbol Digit Modalities Test; MSIS-29 = Multiple Sclerosis Impact Scale; std = standard deviation; Definitions of disease and drug use characteristics can be found in Supplemental table S2.

region (Nordic/non-Nordic); highest achieved education level; use of antidepressants, antipsychotics, antidiabetics, glucocorticoids, immunosuppressive agents, and systemic hormonal contraceptives (females only) in the previous 5 years; arrhythmia and major acute cardiovascular event diagnoses in the previous 5 years; parity (females only); history of any invasive cancer and the specified outcome cancer (if applicable) during and before the previous 5 years; number of hospital days in the previous 5 years; presence of sick leave and disability pension the previous year; and MS type, disease duration, number of previous therapies, previous interferon, previous glatiramer acetate, Expanded Disability Status Scale (EDSS), Symbol Digit Modalities Test (SDMT), and MS Impact Scale (MSIS-29) for patients in the MS register (all times relative to start of therapy). For definitions of the drug-use and diagnosis covariates, see Supplementary Table S2.

Statistical Analysis

For all outcomes, we calculated the number of events, person-time, and incidence rates (IR; estimated by Poisson regression when adjusted by weighting) with 95% confidence intervals (CI), stratified by cohort. For any invasive cancer, basal-cell carcinoma, and CIN3, we also estimated hazard ratios (HR) and 95% CIs using Cox regression with robust standard errors (to account for both the weighting and that subjects could contribute to more than 1 cohort) and time since therapy start as the time scale. For the other outcomes, the number of events were insufficient to perform regression analysis. The largest group was chosen as the reference, in accordance with the prespecified study plan (rituximab for the within-MS analyses and the general population otherwise).

Missing data were addressed using multiple imputation with the fully conditional specification method[23] and

25 imputations with 30 burn-in iterations. Imputation models for each covariate included all other covariates, with categorization and polynomial terms as used in later analyses, the specific event, and the Nelson-Aalen estimator of the cumulative hazard substituting the time to event.[24] As the event was part of the models, separate imputations had to be made for each outcome. Additionally, an indicator for being part of a previous chart review of the MS register was included in the imputation model, as this was associated with having fewer missing data.[17]

We assessed differences in pretreatment covariates between the exposure groups and used stabilized inverse probability of treatment weighting (IPTW) in the Poisson and Cox regressions to adjust for any imbalances.[25–27] Weights were derived from propensity scores calculated using multinomial logistic regression as the inverse of the model-predicted probability of receiving the treatment that the subject had in fact received and stabilized by multiplication with the marginal population proportion receiving the same therapy. Continuous variables were modelled as second (EDSS), third (age, disease duration), or fourth (SDMT, MSIS-29) grade polynomials. All other variables were categorical. The choice of polynomial was influenced by the fit of the propensity score models and after iteratively reviewing the achieved balance in terms of the standardized mean difference to the pooled population. Age was adjusted for in a doubly robust way by being included as a covariate in the Cox models in addition to the weighting. The IPTW and Cox regressions were performed for each imputed dataset in the analyses and the HRs pooled using Rubin's rules.[28] The standardized mean difference was assessed for each covariate, before and after weighting, to assert that balance between the groups had been achieved.

All statistical analyses were done using Python 3.6.6[29] and R 3.5.1.[30] Multiple imputation was done using the mice R package,[31] propensity score calculations using the nnet R package,[32] and Cox regression using the survival R package.[33]

TABLE 2A. Number at Risk, Events, Person-Years, and Crude/Weighted Incidence Rates, Stratified by Cancer Type and Cohort

Outcome/Therapy	Number at risk	Number of events	Person-years	IR/10 000 py (95% CI)	W. IR*/10 000 py (95% CI)
Any invasive					
Rituximab	4187	33	9597.2	34.4 (23.7–48.3)	29.1 (20.1–42.1)
Fingolimod	1620	28	6370.9	44.0 (29.2–63.5)	48.9 (34.2–69.9)
Natalizumab	1670	17	6536.8	26.0 (15.1–41.6)	42.3 (28.4–63.0)
General population	37801	353	113970.5	31.0 (27.8–34.4)	—
Basal cell					
Rituximab	4187	20	9601.9	20.8 (12.7–32.2)	17.0 (10.4–27.6)
Fingolimod	1620	15	6382.5	23.5 (13.2–38.8)	18.0 (10.0–32.3)
Natalizumab	1670	8	6560.5	12.2 (5.3–24.0)	15.4 (8.1–29.3)
General population	37801	145	114333.2	12.7 (10.7–14.9)	—
CIN3 (females)					
Rituximab	2968	15	6729.8	22.3 (12.5–36.8)	23.6 (14.5–38.6)
Fingolimod	1104	17	4347.9	39.1 (22.8–62.6)	33.2 (19.7–55.9)
Natalizumab	1215	15	4793.0	31.3 (17.5–51.6)	24.0 (13.2–43.8)
General population	26699	204	80369.4	25.4 (22.0–29.1)	—

*The general population was not part of weighted analyses and weights were calculated using our most fully adjusted model: age, sex, birth region, education, previous invasive cancer, arrhythmia, major acute cardiovascular event, use of antidepressants, antipsychotics, antidiabetics, glucocorticoids, and immunosuppressives, hospital days, sick leave, disability pension, MS type, disease duration, number of previous therapies, previous interferon, previous glatiramer acetate, EDSS, SDMT, and MSIS-29.

Notes: IR = Incidence Rate; W = Weighted; py = person years; CI = Confidence Interval; CIN3 = Cervical Intraepithelial Neoplasia.

TABLE 2B. Number at Risk, Events, Person-Years, and Crude/Weighted Incidence Rates, Stratified by Cancer Type and Cohort

Outcome/Therapy	Number at risk	Number of events	Person-years	IR/10 000 py (95% CI)	W. IR*/10 000 py (95% CI)
Breast (females)					
Rituximab	2968	6	6744.0	8.9 (3.3–19.4)	6.9 (2.8–17.1)
Fingolimod	1104	4	4381.0	9.1 (2.5–23.4)	7.5 (2.5–22.2)
Natalizumab	1215	2	4823.7	4.1 (0.5–15.0)	2.6 (0.4–16.1)
General population	26699	114	80573.8	14.1 (11.7–17.0)	—
Prostate (males)					
Rituximab	1219	2	2884.3	6.9 (0.8–25.0)	5.7 (1.3–26.1)
Fingolimod	516	3	2024.9	14.8 (3.1–43.3)	37.1 (17.5–78.9)
Natalizumab	455	0	1751.0	0.0 (0.0–21.1)	0.0 (0.0–inf)
General population	11102	20	33796.6	5.9 (3.6–9.1)	—
Melanoma					
Rituximab	4187	4	9630.8	4.2 (1.1–10.6)	3.1 (1.0–9.7)
Fingolimod	1620	4	6410.4	6.2 (1.7–16.0)	4.6 (1.5–14.5)
Natalizumab	1670	2	6572.9	3.0 (0.4–11.0)	2.3 (0.4–12.2)
General population	37801	35	114533.7	3.1 (2.1–4.2)	—
NMSC					
Rituximab	4187	3	9630.5	3.1 (0.6–9.1)	2.2 (0.6–8.4)
Fingolimod	1620	3	6414.1	4.7 (1.0–13.7)	11.1 (5.0–24.9)
Natalizumab	1670	0	6576.4	0.0 (0.0–5.6)	0.0 (0.0–inf)
General population	37801	15	114591.2	1.3 (0.7–2.2)	—
Lymphoma					
Rituximab	4187	1	9634.6	1.0 (0.0–5.8)	1.0 (0.1–7.4)
Fingolimod	1620	2	6414.8	3.1 (0.4–11.3)	2.9 (0.7–12.4)
Natalizumab	1670	0	6576.4	0.0 (0.0–5.6)	0.0 (0.0–inf)
General population	37801	10	114591.0	0.9 (0.4–1.6)	—

*The general population was not part of weighted analyses and weights were calculated using our most fully adjusted model: age, sex, birth region, education, previous invasive cancer, arrhythmia, major acute cardiovascular event, use of antidepressants, antipsychotics, antidiabetics, glucocorticoids, and immunosuppressives, hospital days, sick leave, disability pension, MS type, disease duration, number of previous therapies, previous interferon, previous glatiramer acetate, EDSS, SDMT, and MSIS-29.

Notes: IR = Incidence Rate; W = Weighted; py = person years; CI = Confidence Interval; NMSC = Non-Melanoma Skin Cancer.

Sensitivity Analyses

We had 3 prespecified sensitivity analyses. Because age was expected to be the strongest potential confounder (due to its strong association with cancer risk), we performed an alternative analysis using age as the time scale in the Cox models (with delayed entry, so that each subject entered the analysis with the age at their index date) to minimize residual confounding by age due to the parametrizations used in the propensity score models. In a second alternative analysis, we introduced a lag time (6 months) for when outcomes started to be measured after therapy start to limit any effects of previous therapies. We also tested the sensitivity to the

ever-treated exposure window by using an on-treatment approach to follow-up (patients were considered exposed between therapy start and 3 months after therapy stop) and, in the same analysis, restricting the therapy starts to the first of either of the therapies (ie, no previous exposure to the other therapies were allowed) in an attempt to capture only the effects of the active treatment. In post hoc analyses, we further investigated the sensitivity to large weights generated by the IPTW by limiting the maximum value of the stabilized weights to the 99th percentile of their original values and the sensitivity to the missing-at-random assumption of the multiple imputation, using the weighting method described by Carpenter et al[34] with delta values chosen according to Héraud-Bousquet et al.[35]

Results

We included 6,136 MS patients with 7,477 therapy initiations: 4,187 rituximab (average follow-up = 2.30 years), 1,620 fingolimod (average follow-up = 3.96 years), and 1,670 natalizumab (average follow-up = 3.94 years), matched to 37,801 non-MS general population subjects (average follow-up = 3.03 years).

There were differences in several of the baseline characteristics between the therapy groups (Table 1A and 1B), most notably for age (oldest for rituximab and youngest for natalizumab), disease duration (shortest for natalizumab), disability pension (highest for rituximab and lowest for natalizumab), hospital days (higher for fingolimod), MS type (more SPMS and PPMS for rituximab), previous interferon or glatiramer acetate (both more common for fingolimod), MSIS-29 and EDSS (highest for rituximab and lowest for fingolimod), SDMT (highest for fingolimod), and number of previous therapies. The general population comparator subjects had less use of antidepressants and glucocorticoids and less disability pension and sick leave but were otherwise close to an average of the treated groups (Supplementary Table S3). The differences between therapies were balanced by the IPTW, resulting in standardized mean differences to the pooled population of less than 0.1 for all variables in all 3 therapy groups (Supplementary Table S4). Distributions of the IPTW weights are shown in Supplementary Tables S5 to S7. Missing data were negligible for all variables except those from the MS register, where EDSS was missing in 31 to 36% of all therapy episodes, and SDMT/MSIS-29 was missing in 16 to 19% of fingolimod/natalizumab therapy episodes and 47 to 48% of rituximab therapy episodes (Supplementary Table S8).

Without adjusting for baseline covariates, we found numerically higher IRs (per 10,000 person-years) for fingolimod compared to the other cohorts for most outcomes (Table 2A and 2B). The IR of invasive cancer in the fingolimod group was 44.0 (95% CI = 29.2–63.5), compared to 34.4 (95% CI = 23.7–48.3) for rituximab, 26.0 (95% CI = 15.1–41.6) for natalizumab, and 31.0 (95% CI = 27.8–34.4) for the general population.

Adjusting for demography, previous cancer, and comorbidities using IPTW in a Cox regression with the general population as the reference (Figure), the risk of invasive cancer was similar or slightly lower for natalizumab (HR = 1.01, 95% CI = 0.57–1.77) and rituximab (HR = 0.85, 95% CI = 0.54–1.32) and numerically higher for fingolimod (HR = 1.53, 95% CI = 0.98–2.38).

The influence of specific sets of confounders is shown in Table 3 (with rituximab as reference to allow for adjustment for MS-specific covariates). As expected, the inclusion of age as a covariate in the models had the biggest impact because age is a strong predictor of cancer risk and varied between the groups. These incremental models start with crude HRs for invasive cancer of 1.26 (95% CI = 0.79–2.00) for fingolimod, 0.74 (95% CI = 0.42–1.30) for natalizumab, and 0.89 (95% CI = 0.62–1.28) for the general population, compared to rituximab. Adjusting for age and other demographic factors, the HRs for invasive cancer were 1.78 (95% CI = 1.05–3.03) for fingolimod, 1.34 (95% CI = 0.73–2.49) for natalizumab, and 1.18 (95% CI = 0.81–1.73) for the general population. These numbers remained stable after adjusting for further covariates, and in our most fully adjusted model, estimated HRs for invasive cancer were 1.68 (95% CI = 1.00–2.84) for fingolimod and 1.36 (95% CI = 0.78–2.36) for natalizumab, compared to rituximab. Changing the reference to natalizumab resulted

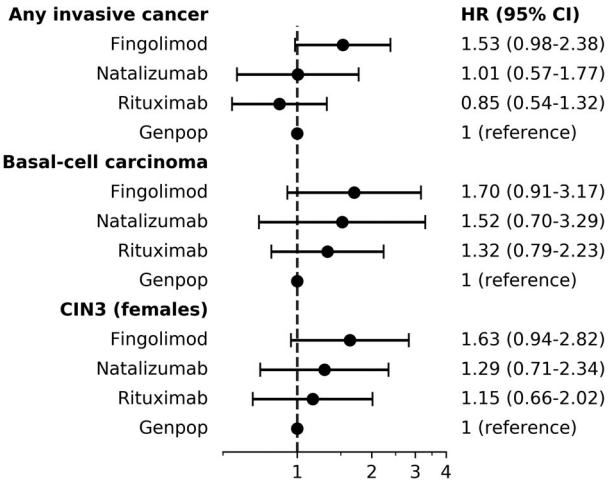

FIGURE: Hazard ratios (HR) and 95% confidence intervals (CI) from inverse probability of treatment weighting–adjusted Cox regression models, with the general population as the reference and time since therapy start as the time scale. Adjusted for age, sex, birth region, education, previous invasive cancer, arrhythmia, major acute cardiovascular event, and use of antidepressants, antipsychotics, antidiabetics, glucocorticoids, and immunosuppressive agents. CIN3 = cervical intraepithelial neoplasia.

TABLE 3. Hazard Ratios and 95% Confidence Intervals from Incrementally Adjusted Cox Regression Models Using Inverse Probability of Treatment Weighting

Outcome/Model	Fingolimod	Natalizumab	General population
Any invasive			
Crude[a]	1.26 (0.79–2.00)	0.74 (0.42–1.30)	0.89 (0.62–1.28)
+Demography[b]	1.78 (1.05–3.03)	1.34 (0.73–2.49)	1.18 (0.81–1.73)
+Cancer[c]	1.79 (1.05–3.04)	1.30 (0.71–2.38)	1.19 (0.81–1.74)
+Comorbidities[d]	1.80 (1.07–3.04)	1.19 (0.61–2.30)	1.18 (0.76–1.84)
+Health and MS[e]	1.68 (1.00–2.84)	1.36 (0.78–2.36)	—
Basal cell			
Crude[a]	1.11 (0.58–2.13)	0.58 (0.27–1.23)	0.60 (0.38–0.97)
+Demography[b]	1.37 (0.68–2.75)	1.13 (0.52–2.47)	0.77 (0.47–1.24)
+Cancer[c]	1.39 (0.68–2.81)	1.02 (0.45–2.29)	0.75 (0.46–1.22)
+Comorbidities[d]	1.28 (0.60–2.74)	1.15 (0.49–2.69)	0.75 (0.45–1.27)
+Health and MS[e]	1.11 (0.51–2.40)	0.91 (0.40–2.06)	—
CIN3 (females)			
Crude[a]	1.80 (0.96–3.37)	1.48 (0.80–2.74)	1.17 (0.68–1.98)
+Demography[b]	1.51 (0.80–2.83)	1.14 (0.58–2.26)	1.03 (0.60–1.75)
+Cancer[c]	1.54 (0.82–2.90)	1.16 (0.59–2.30)	1.04 (0.61–1.78)
+Comorbidities[d]	1.41 (0.72–2.77)	1.12 (0.55–2.26)	0.87 (0.50–1.51)
+Health and MS[e]	1.21 (0.58–2.50)	0.93 (0.42–2.04)	—

Rituximab as the reference and time since therapy start as the time scale. Each model also contains all variables from the previous models.

[a]No covariates.

[b]Age, sex, birth region, education.

[c]Any invasive cancer and the specified outcome cancer before therapy start (if applicable).

[d]Arrhythmia, major acute cardiovascular event, parity (females), and use of antidepressants, antipsychotics, antidiabetics, glucocorticoids, immunosuppressive agents, and systemic hormonal contraceptives (females).

[e]Hospital days, sick leave, disability pension, MS type, disease duration, number of previous therapies, previous interferon, previous glatiramer acetate, EDSS, SDMT, and MSIS-29.

CIN3 = cervical intraepithelial neoplasia; MS = multiple sclerosis; EDSS = Expanded Disability Status Scale; SDMT = Symbol Digit Modalities Test; MSIS-29 = Multiple Sclerosis Impact Scale.

in HRs of 1.23 (95% CI = 0.72–2.12) for fingolimod and 0.73 (95% CI = 0.42–1.27) for rituximab (Supplementary Table S9).

We found no differences in risk of basal-cell carcinoma (fingolimod: HR = 1.11, 95% CI = 0.51–2.40; natalizumab: HR = 0.91, 95% CI = 0.40–2.06) or CIN3 (fingolimod: HR = 1.21, 95% CI = 0.58–2.50; natalizumab: HR = 0.93, 95% CI = 0.42–2.04) compared to rituximab. For the other outcomes, the number of events was too low (0–6) for statistical modelling in the treated groups.

In a post hoc tabulation of each individual event that was observed for the any-invasive-cancer outcome, 23 different types of cancer were observed among the MS patients, with the 6 most common overall being breast, melanoma, colon, other endocrine glands and tissues, nonmelanoma skin, and prostate cancers (Table 4).

In our sensitivity analyses, when using age as the time scale in the Cox regression and when introducing a lag time to follow-up, HRs were similar to the main analysis, although slightly higher when comparing fingolimod to rituximab (Supplementary Tables S10–S12). Using the on-treatment approach to follow-up and limiting the analysis to the first of the studied therapies for each patient also gave the same conclusions, but with a numerically

TABLE 4. Types of Cancer Making Up the Outcome of Any Invasive Cancer

Cancer Type	Rituximab	Fingolimod	Natalizumab
Breast	6	4	2
Melanoma	4	4	2
Colon	4	3	3
Other endocrine glands and tissues	1	3	3
Nonmelanoma skin	3	3	0
Prostate	2	3	0
Malignant lymphoma	1	2	0
Corpus uteri	0	1	2
Lung and bronchus	2	0	0
Bladder	2	0	0
Anus and anal canal	1	0	1
Kidney	1	0	1
Pancreas	1	1	0
Testicle	0	1	1
Brain	1	0	1
Thyroid	0	1	0
Rectum	0	0	1
Liver and intrahepatic bile duct	1	0	0
Leukemia	1	0	0
Digestive organs	1	0	0
Cervix uteri, collum uteri, portio	0	1	0
Bone, joint, and cartilage in the extremities	0	1	0
Vagina	1	0	0

more pronounced risk increase for fingolimod versus rituximab (HR = 3.43, 95% CI = 1.65–7.13; Supplementary Tables S13 and S14). The post hoc analysis testing the sensitivity to large weights in the IPTW also gave very similar results to the main analysis, although with modestly increased risks of invasive cancer for fingolimod compared to both the general population and rituximab, reaching statistical significance for both (Supplementary Tables S15 and S16). Finally, the post hoc analysis testing the sensitivity to the missing-at-random assumption of the multiple imputation showed no difference when the results were weighted to emulate a missing-not-at-random scenario for each of the 4 variables with the most missing data (Supplementary Table S17).

Discussion

In this large real-world study investigating cancer risks of 3 highly effective MS DMTs, we found cancer rates that were overall similar to the rates among the MS-free general population, with no evidence of an increased risk for rituximab or natalizumab. However, we found a borderline-significant increased risk of invasive cancer for fingolimod, compared to both the general population and rituximab, after adjustment for differences in baseline characteristics. For basal-cell carcinoma and CIN3, we could not detect any differences between the studied therapies and there were also no clear imbalances in cancer subtypes across the therapies, within the any-invasive-cancer outcome.

Studies investigating the risk of cancer in MS populations compared to non-MS populations, without specifically contrasting different DMTs, report a slightly lower incidence of cancer in persons with MS compared to the general population, with the exception of certain cancer types such as tumors of the brain and urinary organs.[36,37] Hypothesized reasons for the lower cancer risk in MS patients include diagnosis neglect, behavioral changes, and therapy effects, as well as immunologic characteristics of MS improving cancer surveillance.[36,37] In this study, we found a similar risk of cancer for the general population and MS patients treated with rituximab or natalizumab and a numerically higher risk for MS patients treated with fingolimod, compared to the general population (see Figure).

Because rituximab is used off-label for MS, there is only limited data on its safety for this indication. However, our findings here are in line with those obtained from its use in RA, where a long-term (9.5 years) follow-up of the global clinical trials program found no evidence for an increased risk of cancer linked to ever use or accumulated exposure of rituximab.[38] Similarly, a large observational study recently found no increased risk of cancer for rituximab compared to other biological RA drugs.[39] We observed 6 breast cancers in our rituximab cohort, corresponding to an IR of 8.9 per 10,000 person-years (95% CI = 3.3–19.4), which was not significantly different from the rate in the general population. Although it is well known that randomized controlled trials have limited ability to detect rare safety outcomes such as cancer, it is interesting to contrast these observations with those from the pivotal studies for ocrelizumab, another anti-CD20 drug that was recently approved for MS, where more breast cancer was reported for ocrelizumab than for placebo, with IR 26.1 versus 0 per 10,000 person-years.[40]

For natalizumab, its 2 pivotal trials reported comparable numbers of cancer between the active and control groups,[4,5] and postmarketing surveillance also gives no indication of an increased cancer risk.[22] Our finding that natalizumab had a cancer rate comparable to the general population supports this conclusion in a larger population of unselected patients treated in clinical practice.

For fingolimod, both the US Food and Drug Administration label and European Medicine Agency (EMA) product information include lymphoma as a possible adverse effect, based on data from premarketing clinical trials, and the EMA further includes a warning for cutaneous cancers. The pivotal trials for fingolimod and their long-term follow-up have given inconclusive reports of cancer risk,[6,7,41–44] but taken together an increased risk of cancer cannot be excluded. These studies lacked comparisons to other highly effective MS DMTs, however, and did not include the full range of patients that are treated in clinical practice. We observed a borderline-significant increase in risk of cancer for patients treated with fingolimod, with a magnitude corresponding to a 50% increased risk compared to the general population's rate of cancer. We did not observe any particular pattern of specific cancer between the different therapies, and we found no difference in risk when looking specifically at basal-cell carcinoma and CIN3. In preclinical studies, fingolimod/sphingosine-1-phosphate receptor modulators have been attributed both pro- and antioncogenic effects[45] and have even been investigated as potential antitumor drugs.[46] However, fingolimod may also affect tumorigenicity through immunosuppressive effects.[46] In particular, fingolimod's systemic effects on both CD4 and CD8 T cells are different from those observed with natalizumab or rituximab. Further studies with even larger populations and longer follow-up will be needed to confirm or reject our findings and to investigate potential differences in risk of specific cancer types.

A major strength of this study is the high quality of the data sources used; the Swedish registers have virtually complete national coverage and a proven high completeness and validity. These registers make it possible to follow patients without attrition and are therefore ideal for studying rare safety outcomes in a population-based setting. By linking the national registers to the Swedish MS register, we were able to include almost all of Sweden's MS patients treated with rituximab, fingolimod, or natalizumab, limiting the risk of selection bias and allowing for our results to be generalized to the entire Swedish MS population treated with these drugs. The register linkage also allowed us to adjust for many important confounders. Despite this, residual confounding might still be an issue. Specifically, we had no data on diet, alcohol use, workplace exposure to carcinogens, obesity, sunlight exposure, or, importantly, smoking, all of which are well-known risk factors for cancer. Although an association of these variables with the choice of therapy is not likely, we cannot with certainty exclude them as potential confounders. Several general health markers and demographic variables were included in an effort to limit unmeasured confounding by proxy. Another limitation of the study is the insufficient power to compare the risks of many of the specific cancer types due to their rarity. However, reporting of IRs for these outcomes can still be of value for replication in other cohorts or in meta-analyses.

In conclusion, using population-based nationwide data, we found no evidence for an increased risk of invasive cancer in MS patients treated with natalizumab or rituximab. However, we found borderline-significant higher risks of invasive cancer in MS patients treated with fingolimod compared to both the general population and

rituximab. Collectively, cancer risks with the 2 studied biologics, natalizumab and rituximab, seem to be similar to the general population, and a possible modest increase in risk with fingolimod needs to be validated in studies with larger cohorts followed over longer periods of time.

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Author Contributions

P.A., F.P., and T.F. participated in the study concept and design and drafting of the manuscript. P.A. and T.F. did the statistical analysis. All authors participated in data acquisition, interpretation of the data, and critical revision of the manuscript.

Potential Conflicts of Interest

J.A.: principal investigator (PI) in agreements between Karolinska Institute and Roche, mainly regarding safety monitoring of immune-modulatory drugs in rheumatology; A.F.-H.: unrestricted research grants, Biogen; J.H.: honoraria, advisory boards, speaking fees, PI for projects or unrestricted research support, Biogen, Novartis; J.L.: travel support, lecture honoraria, scientific advisory boards, unconditional research grants, Biogen, Novartis; P.N.: travel support, Biogen, honoraria, advisory boards, Novartis, Roche, lectures, advisory boards, Biogen, unconditional grants, Biogen; M.V.: unrestricted research grants, Novartis, honoraria, lectures, Biogen, advisory boards, Roche, Novartis; T.O.: honoraria, lectures, advisory boards, unrestricted MS research grants, Biogen, Novartis, Roche; F.P.: research grants, Biogen, Novartis. P.A., J.B., K.F., M.G., A.L.-G., J.S., A.S., and T.F. report no conflicts of interest. Commercial entities relevant for potential conflicts of interest are: Novartis (Fingolimod/Gilenya), Biogen (Natalizumab/Tysabri), and Roche (Rituximab/Mabthera).

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