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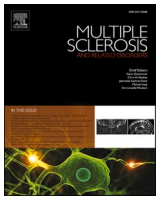

Incidence of cancer in multiple sclerosis before and after the treatment era–a registry- based cohort study

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ABSTRACT

Background: Whether disease-modifying therapies (DMTs) influence cancer in multiple sclerosis (MS) is uncertain.
Objectives: Assess incidence of cancer diagnosis among Norwegian MS patients compared to the general population in 1953 to 1995 and 1996 to 2017-reflecting era before and after introduction of DMTs.
Methods: We performed a nationwide cohort study comprising 6949 MS patients and 37,922 controls, matched on age, sex and county. The cohort was linked to Norwegian Cancer Registry, Cause of Death Registry and National Educational database. We used Poisson regression to calculate incidence rate ratio (IRR) of cancer.
Results: During 1953–1995 MS patients had similar cancer frequency compared to controls (IRR: 1.11 (95% Confidence Intervals (CI): 0.90–1.37)), although MS patients had increased frequency of cancer in endocrine glands (IRR: 2.51 (1.27–4.93). During 1996–2017 we identified significant increased frequency of cancer among MS patients compared to controls (IRR: 1.38 (95% CI: 1.28–1.52): in brain (IRR: 1.97 (1.41–2.78)), meninges (IRR: 2.44 (1.54–3.77)), respiratory organs (IRR: 1.96 (1.49–2.63)). The excess cancer diagnosis was most frequent among MS patients $\geq$ 60 years of age (HR 1.30 (1.15–1.47)).
Conclusion: Incidence of cancer among MS patients compared to controls was higher in 1996 to 2017, corresponding in time to the introduction of DMT for MS. This was observed more frequently among MS patients older than 60 years of age.

1. Introduction

Multiple sclerosis (MS) is the most common cause of neurological disability among young adults. The disease affects more females than males (3:1) and onset of disease is averagely 33 years, followed by lifelong disease modifying therapy (Thompson et al., 2018). MS patients have increased risk of several comorbidities, including cancer, and the life expectancy is averagely eight years shorter than the general population in Norway (Lunde et al., 2017). We have previously reported an increased risk of overall cancer among patients with MS in Norway with follow up from 1953 to 2017, however the reason for the increased risk of cancer among MS patients is still unknown (Grytten et al., 2019).

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The first disease modifying therapies were introduced to MS patients in Norway in 1996, and since 2000, more than fifteen immunosuppressant (IS) drugs have become available. Studies have suggested increased adverse cancer events among patients treated with mitoxantrone, azathioprine and cyclophosphamide (Lebrun and Rocher, 2018). Although studies that confirm cancer risk are lacking, therapies such as cladribine, fingolimod, natalizumab or alemtuzumab are accompanied by warning against potential cancer risk due to their effects on the immune system (Rae-Grant et al., 2018). For treatment with fingolimod, natalizumab, alemtuzumab, dimethyl fumarate, teriflunomide, daclizumab, and ocrelizumab, a risk management plan for cancer monitoring is mandatory. One recent study found a possibly modest higher risk of cancer in patients treated with fingolimod, but not in patients treated with natalizumab and rituximab (Alping et al., 2020).

During the last 60 years, survival has improved among MS patients (Lunde et al., 2017) Longer life expectancy can contribute to increased cancer prevalence due to older age and shared risk factors between MS and cancer, like smoking. In addition, the clinical services to follow up MS disease has improved and the ability to detect cancer during MS scans of the brain has increased considerably.

The objectives of our study were to assess the incidence of cancer diagnosis among Norwegian MS patients compared to the general population during 1953 to 1995 and during 1996 to 2017 in a large nationwide cohort - before and after DMTs became routinely available in Norway. We hypothesized that MS patients could have an altered incidence of cancer diagnosis after 1996.

2. Methods

The patients were retrieved from the Norwegian Multiple Sclerosis Registry and Biobank, and in a sample study of epidemiological data on MS patients born between 1930 and 1979, which were retrieved from previous published prevalence studies (Kampman et al., 2013). All patients were diagnosed according to the criteria of Poser or McDonald as described in a previous study using the same cohort of patients (Kampman et al., 2013). Data on up to six non-MS controls matched to every MS patients on sex, year of birth and area of residence were retrieved from Statistics Norway. The complete cohort of MS cases (n=6949) and population controls (n = 37,922) were linked to the Norwegian Cancer Registry, the Cause of Death Registry and the National Education Database. In the Norwegian Cancer Registry, the incident malignant cases have been mandatory registered since 1953, which is the start of follow-up in this study. All malignant cases diagnosed between 1953 and 2017, the date of cancer diagnosis and the type and site of malignancy were extracted for the cohort of MS patients and controls. Table 4 appendix, shows ICD-10 codes, converted from ICD 6–9, which have been used to identify cancer diagnosis in the analysis. The primary outcome was time to first diagnosis of cancer.

For any cancer outcomes, we calculated the number of events, person- time and incidence rate ratios (IRR) estimated by Poisson regression with 95% confidence intervals (CI). This regression model is a generalized linear model assuming a Poisson probability distribution, modeling the rare events – such as cancers – occurring independently in a given time-period. Each parameter in this model is estimated using the maximum likelihood method. The IRR is the ratio of two incidence rates, which is the number of events divided by the person-time at risk. Offset variable was person- time (years) until end of follow-up due to death, emigration, end of study period, or causes of loss of follow-up during 1953 to 1995, and 1996 to 2017. We used adjusted Cox proportional hazard regression (reported as hazard ratios (HRs) with 95% CIs) to estimate the association of cancer risk in patients below or above 60 years of age.

Covariates were categorized as male (1), female (2), cancer diagnosis (Y/N = 1/0), attained educational levels into primary (10 years or less), secondary (11–13 years), undergraduate (14–17 years), graduate (18 years or more), age was treated as continuous. IRRs were estimated by strata of sex and the estimations were adjusted for age at start of follow-up, county of residence and attained educational level. IRRs were estimated for all site-specific cancers excluding basal cell carcinoma, which is not available in the Norwegian Cancer Registry, sex, and periods of cancer diagnosis 1953–1995 and 1996–2017.

The at-risk-period for a cancer event started on 1. January 1953 (the beginning of The Norwegian Cancer Registry Coverage), and ended with time of diagnosis of cancer, death, emigration or 31. December 2016, whichever came first. The at-risk-period until 1996 started with following cases being alive at 1. January 1953 and subsequently included by birth and excluded by emigration and death and ended 31. December 1995, whichever came first. The at-risk-period until 2017 started with all cases being alive on 1. January 1996 and included by birth and excluded by emigration or death until 1. January 2017, whichever came first. Table 1 shows demographic and clinical characteristics of the sample. Cases being alive, not emigrated nor having cancer diagnosis in 1995 were followed- up continuously until 2017.

Descriptive statistics were performed by using IBM SPSS Statistics 24 (IBM corp., Armonk, N.Y., USA) and incidence rate ratio calculations were carried out by using Stata Statistical Software: Release 15 (StataCorp, College Station, TX, USA).

Ethical approval was provided by The Western Norway Regional Committee for Medical and Health Research Ethics (REK Vest 2016/300).

3. Results

3.1. Total cancer risk from 1953 to 2017

For the total period of follow-up, we calculated 3,79,868 person years of follow- up among 6949 MS patients and 2,110,642 person years among 37,918 controls. In total, we identified 4805 incident cancer cases, of whom 788 were MS patients and 4017 were controls.

The total adjusted cancer incidence rate ratio (IRR) among MS patients compared to controls was 1.35 (95% confidence intervals (CI): 1.25–1.45). Among female MS patients the cancer risk was IRR: 1.35 (1.23–1.49) compared to female controls, and among male MS patients the cancer risk was IRR: 1.41 (1.18–1.54) compared to male controls. Mean age at overall cancer diagnosis was similar with 57.0 years (SD: 12.0) for MS patients (n = 774) and 58.0 years (SD: 13.8) for controls (n = 4017) (ANOVA t-test p = 0.11).

3.2. Cancer risk from 1953 to 1995

For the period 1953–1995 we calculated 254,088 person years of follow- up among patients and 1 370,882 among controls. We identified 964 incident cancer cases of whom 155 were MS patients and 807 were controls.

From 1953 to 1995 the total cancer risk was slightly, although not significantly increased among MS-patients compared to controls (IRR: 1.11, 95% CI: 0.90, 1.37) (Table 2). Among female MS patients the cancer risk was IRR: 1.27 (1.01, 1.59) compared to female controls, and among male MS patients the cancer risk was IRR: 0.68 (0.41, 1.13) compared to male controls (Fig. 1). A higher age was observed in MS patients who had 42.5 years as mean age (SD: 11.7) at overall cancer diagnosis in comparison to controls who had 38.3 as mean age at overall cancer diagnosis (n = 529) (ANOVA t- test p = 001). Mean age at cancer diagnosis was 36.2 (SD: 10.1) years for male MS patients and 37.0 (SD: 13.5) years for male controls. Mean age at cancer diagnosis was 43.6 (SD: 11.6) years for female MS patients and 38.7 (SD: 11.8) years for female controls.

Although no significant overall cancer risk was observed, and numbers were low, we found increased cancer risk among female MS patients in endocrine glands (IRR: 2.51, 95% CI: 1.27, 4.93), and in bones, joints and mesothelium (IRR: 6.28 (1.37–28.65) and increased risk of cancer among male MS patients in urinary organs (IRR: 10.41

Table 1
Number of MS patients and the Norwegian general population controls with follow up 1953 to 2017, with follow up of cancer 1953 to 1995, and with follow up of cancer from 1996 to 2017.

	1953 to 1995				1996 to 2017			
	MS patients		Controls		MS patients		Controls	
	All (n = 721)	Cancer (n = 155)	All (3566)	Cancer (n = 807)	All (n = 6228)	Cancer (n = 623)	All (n = 34,352)	Cancer (n = 3210)
Sex; n (%):								
Female	488 (68)	127 (82)	2513 (70)	603 (75)	4150 (67)	410 (66)	22,751(66)	2014 (63)
Male	233 (32)	28 (18)	1053 (30)	204 (25)	2078 (33)	213 (34)	11,601 (34)	1196 (37)
Age at start of follow-up (years); median, (range)	0 (28)	5 (23)	0 (23)	5 (23)	40 (54)	48 (48)	40 (49)	48 (49)
Year of birth; median, (range)	1956 (54)	1956 (54)	1948 (39)	1956 (49)	1948 (49)	1956 (54)	1949 (48)	1956 (49)
Age at cancer diagnosis (years); mean (SD)		42.5 (11.7)		38.3 (12.3)		58.3 (10.50)		59.7 (11.6)
Educational level:								
Primary	161 (22)	40 (26)	859 (24)	205 (25)	1448 (23)	180 (29)	8322 (24)	834 (26)
Secondary	294 (41)	65 (42)	1202 (34)	342 (42)	3039 (49)	303 (49)	14690 (43)	1489 (46)
Undergraduate level	186 (26)	32 (21)	1141 (32)	210 (26)	1326 (21)	100(16)	8997 (26)	682 (21)
Graduate level	62 (9)	17 (11)	364 (10)	50 (6)	381 (6)	38(6)	2343 (0.07)	200 (6)
Not available	18 (2)	1 (1)	7 (0.2)	0	44 (1)	2 (0.3)	0	5 (0.2)

Table 2
Incidence rate ratio (IRR) with 95% Confidence Interval (CI) by Poisson regression for cancer among MS patients compared to controls stratified by sex. Male MS patients and female MS patients compared to male controls and female controls with follow up from 1953 to 1995.

	Men (n = 14,965) Cancer (n)			Women (n = 29,902) Cancer (n)			Total (n = 44,867) Cancer (n)		
	MS	*Control*	*IRR (95% CI)*	*MS*	*Control*	*IRR (95% CI)*	*MS*	*Control*	*IRR (95% CI)*
n	2311	12,654		4638	25,264		6949	37,918	
Person years	85,451	4,62,256 åpxflb2,256		168,637	908,626		2,54,088	1,370,882	
All cancer	28	204	0.68 (0.41, 1. 13)	127	603	1.27 (1.01, 1.59)*	155	807	1.11 (0.90, 1.37)
Brain; nervous system	1	24	5.85 (0.75, 45.45)	8	46	0.68 (0.20, 3.20)	9	70	0.83 (0.28, 2.45)
Meninges	0	1	NA	5	14	0.74 (0.08, 6.49)	5	15	0.71 (0.08, 6,25)
Breast	0	0	NA	32	142		32	142	0.76 (0.49, 1.22)
Skin	7	31	2.08 (0.65,6.54)	16	101	0.51 (0.25,1.06)	23	132	0.69 (0.38, 1.28)
Female genital organs	-	-	NA	26	159	0.78 (0.48,1.27)	26	159	NA
Male genital organs	7	59	0.37 (0.072, 1.77)	-	-	NA	7	59	NA
Eye and adnexa	0	2	NA	0	3	NA	0	5	NA
Urinary organs	6	15	10.41 (2.33, 47.61)*	6	17	1.27 (0.41,3.93)	12	32	2.08 (0.88, 4.87)
Digestive system	3	18	1.19 (0.14,10.20)	11	42	0.81 (0.38,1.73)	14	60	0.84 (0.41, 1.72)
Bones, joints, mesothelium	1	8	16.94 (0.10,1.89)	4	4	6.28 (1.37, 28.65)*	5	12	0.80 (0.38, 1.73)
Endocrine glands	0	8	NA	14	39	2.69 (1.34, 5.36)*	14	47	2.51 (1.27, 4.93)*
Hematological cancers†	2	27	6.67 (1.24, 35.84) *	5	40	0.74 (0.25, 2.20)	7	67	1.06 (0.43, 2.63)
Oral cavity and larynx	0	8	NA	1	4	1.15 (0.11, 12.19)	1	12	0.96 (0.11, 8.14)
Respiratory organs	1	3	NA	3	3	NA	4	6	NA
Unknown	0	1	NA	1	3	NA	1	4	NA

†Lymphoid, hematopoietic and related tissue;
* $p < 0.05$; Abbreviation NA: Not Applicable due to few cases.

(2.33–47.61), and hematological cancers (IRR: 6.67 (1.24–35.84) compared to controls (Table 2).

3.3. Cancer risk from 1996 to 2017

For the period 1996–2017, we calculated 122,780 person years of follow- up among MS patients and 7,29,765 person years among controls. We identified 3833 incident cancer cases, of whom 623 were MS patients and 3210 were controls.

Incidence of overall cancer diagnosis was higher than expected (IRR: 1.38; 95% CI: 1.28–1.52) (Table 3). Among female MS patients the cancer risk was IRR: 1.36 (1.23–1.51) compared to female controls, and among male MS patients the cancer risk was IRR: 1.49 (1.30–1.72) compared to male controls (Fig. 1). A slightly lower age was observed in MS patients (n = 669) who had 58.3 as mean age (SD: 10.5) in comparison to controls (n = 3488), who had 59.7 as mean age (SD: 11.6) at overall cancer diagnosis (t-test p = 0.003) (Table 1). Mean age at cancer diagnosis was 60.2 (SD: 10.3) years for male MS patients and 62.8 (SD: 11.1) years for male controls. Mean age at cancer diagnosis was 57.2 (SD: 10.3) years for female MS patients and 57.9 (SD: 11.5) years for female controls.

Increased incidence was significant for brain and nervous system (IRR: 1.97 (1.41–2.78), meninges (IRR: 2.44, 1.54–3.77) and respiratory organs (IRR: 1.96, 1.49–2.63). Female MS patients had also increased risk of breast cancer (IRR: 1.24, 1.03–1.49), genital cancer (IRR: 1.40, 1.09–1.80) and cancer in digestive system (IRR: 1.48, 1.13–1.92)

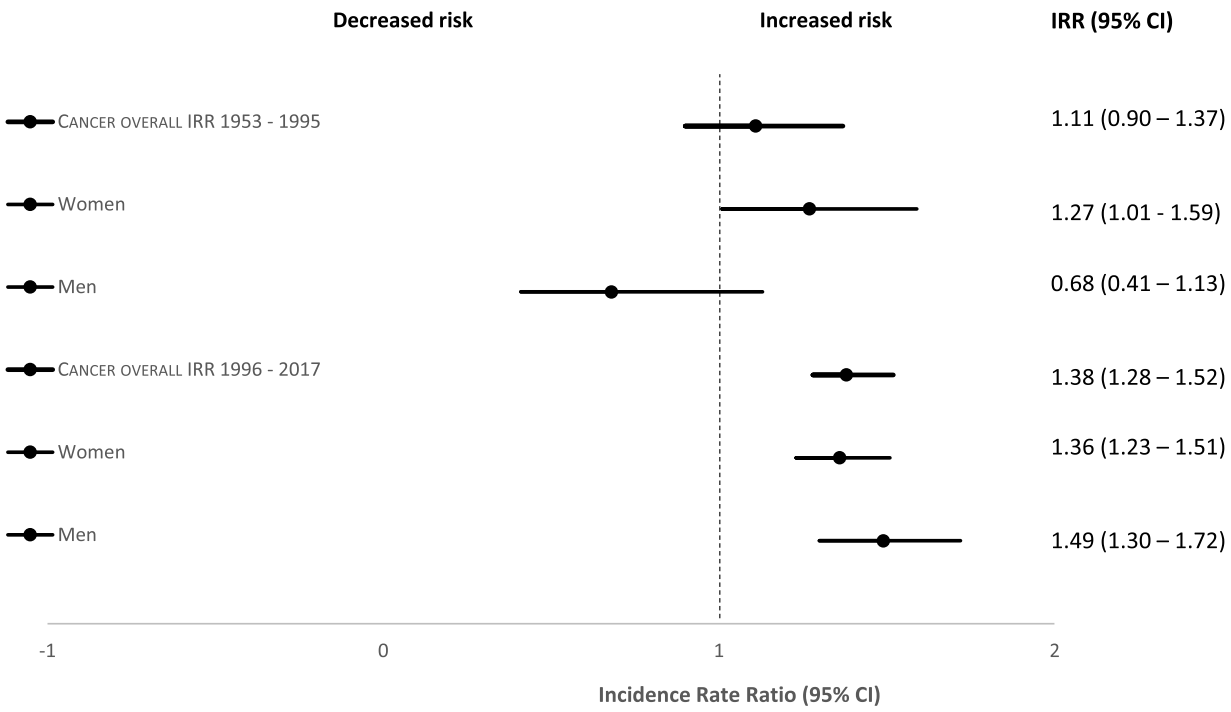

Fig. 1. Forest plot for incidence rate ratio with 95 % Confidence Intervals for cancer diagnosis during 1953–1995 and 1996–2017 among MS patients versus population controls, by sex.

Table 3
Incidence rate ratio (IRR) with 95% Confidence Interval (CI) by Poisson regression for cancer among MS patients compared to controls stratified by sex. Male MS patients and female MS patients compared to male controls and female controls with follow up from 1996 to 2017.

	Men (n = 14,927) Cohort (n)			Women (n = 29,816) Cohort (n)			Total (n = 44,743) Cohort (n)		
	MS	*Control*	*IRR (95% CI)*	*MS*	*Control*	*IRR (95% CI)*	*MS*	*Control*	*IRR (95% CI)*
Cohort: n	2295	12,632		4616	25,200		6911	37,832	
Person years	39,758	243,676		83,022	486,089		122,780	729,765	
All cancer	213	1196	1.49 (1.30, 1.72) **	410	2014	1.36 (1.23, 1.51) **	623	3210	1.38 (1.28, 1.52) **
Brain; nervous system	13	36	2.08 (1.11, 3.38)*	27	84	1.93 (1.32, 2.87) **	40	120	1.97 (1.41, 2.78) **
Meninges	6	8	6.67 (2.22, 18.86)*	16	58	1.98 (1.20, 3.26) *	22	66	2.44 (1.54, 3.77) **
Breast	0	0		129	694	1.24 (1.03, 1.49) *	129	694	
Skin	20	130	1.42 (0.91, 2.22)	32	207	1.16 (0.82, 1.64)	52	337	1.22 (0.94, 1.61)
Female genital organs			-	68	300	1.40 (1.09, 1.80) *	68	300	
Male genital organs	59	434	1.22 (0.94, 1.59)	-	-	-	59	434	
Eye and adnexa	0	5	NA	0	4	NA	0	9	NA
Urinary organs	25	98	2.47 (1.61,3.84) **	18	81	1.57 (0.95, 2.58)	43	179	1.91 (1.38, 2.65) **
Digestive system	34	216	1.37 (0.96,1.97)	65	312	1.48 (1.13, 1.92) *	99	528	1.42 (1.15, 1.76) **
Bones, joints, mesothelium	1	16	0.41 (0.05,3.15)	1	15	0.44 (0.06, 3.33)	2	31	0.41 (0.10, 1.33)
Endocrine glands	3	16	1.15 (0.34,3.86)	9	41	1.16 (0.59, 2.32)	12	57	1.16 (0.65, 2.09)
Hematological cancers[†]	23	99	1.72 (1.09,2.71) *	18	132	0.89 (0.55, 1.45)	41	231	1.19 (0.86, 1.65)
Oral cavity and larynx	4	23	1.22 (0.42,3.57)	4	24	1.10 (0.38, 3.17)	8	47	1.14 (0.54, 2.39)
Respiratory organs	28	112	1.96 (1.29,2.97) *	33	113	2.06 (1.41, 3.03) **	61	225	1.96 (1.49, 2.63) **
Unknown	3	11	1.78 (0.49,6.66)	6	7	7.29 (2.54, 21.27) **	9	18	3.84 (1.77, 8.13) *

[†] Lymphoid, hematopoietic and related tissue;
* $p < 0.05$;
** $p < 0.001$, Abbreviation NA = Not Applicable due to few cases.

compared to female controls. Male MS patients had also increased risk of cancer in urinary organs (IRR: 2.47, 1.61–3.84), hematological cancers (IRR: 1.72, 1.09–2.71) and cancer in respiratory organs (IRR: 1.96 (1.29–2.97) (Table 3).

The excess cancer diagnosis was most frequent among MS patients ≥ 60 years of age: overall cancer HR 1.30 (95% CI: 1.15–1.47), in brain HR: 1.60 (0.85–3.03), respiratory organs HR: 1.98 (95% CI: 1.41–2.79) during 1996–2017.

4. Discussion

We found an increased cancer incidence among MS patients compared to matched controls from the general population during 1996 to 2017, in the era of DMT. In comparison, during 1953 to 1995, before the era of DMT, we did not observe a significantly increased cancer rates among MS patients compared to controls.

With follow- up of cancer from 1996 to 2017, increased incidence of overall cancer and specifically in the brain, meninges and respiratory organs were found both among female and male MS patients. Among

Table 4
Applied ICD-10 codes used to identify cancer diagnosis in the analysis.

Type of cancer	ICD-10
Brain; nervous system	C70, C71, C72
Meninges	C70
Breast	C50
Skin	C43, C44
Female genital organs	C51, C52, C53, C54, C55, C56, C57 + (C58)
Male genital organs	C60, C61, C62
Eye and adnexa	C69
Urinary organs	C64, C65, C66, C67, C68
Digestive system	C15, C16, C17, C18, C19, C20, C21, C22, C23, C24, C25, C26
Bones, joints, mesothelium	C40, C41, C45, C48, C49
Endocrine glands	C73, C74, C75
Hematological cancers[†]	D45, D46, D47, C81, C82, C83, C84, C85, C88, C90, C91, C92, C93, C94, C96
Oral cavity and larynx	C0, C1, C2, C3, C4, C5, C7, C8, C9, C12
Respiratory organs	C30, C31, C32, C33, C34, C37, C38
Unknown	C76, C80

[†] Lymphoid, hematopoietic and related tissue.

female MS patients, the increased incidence of cancer was observed also in breast, genitalia and digestive organs. Among male MS patients, incidence of cancer was more frequently observed in urinary organs and hematological system during the whole follow- up from 1953 to 2017.

Most studies have reported a slightly decreased cancer risk among MS patients compared to controls, with the exception of increased risk of developing malignancies in certain site specific cancer types such as in brain (Grytten et al., 2019, Hofer et al., 2010) urinary organs (Grytten et al., 2019, Bahmanyar et al., 2009, Ajdacic-Gross et al., 2016), malignant melanoma (Hofer et al., 2010, Norgaard et al., 2018, Nielsen et al., 2006), digestive and respiratory organs (Grytten et al., 2019), male and female genitalia, breast (Ajdacic-Gross et al., 2016, Nielsen et al., 2006, Koch-Henriksen, 1999, Sun et al., 2014) and lymphoma (Bahmanyar et al., 2009). The site-specific cancer types have been explained as caused by life style behavior such as smoking, and MRI surveillance resulting in the detection of brain and CNS cancer at an early stage among MS patients (Grytten et al., 2019, Bahmanyar et al., 2009, Kingwell et al., 2012).

By comparing cancer incidence before and after introduction of MS treatment, we found that the previously reported cumulative higher hazard ratio among MS patients compared to the general population (Grytten et al., 2019), is most likely attributional to cancer incidence after 1996. We found especially a higher cancer incidence in brain, meninges, urinary organs and respiratory organs among MS patients in the period 1996 to 2017, after DMT was introduced to MS patients. The increased cancer risk in respiratory and urinary organs could possibly be related to differences in life style behavior such as smoking which are more frequent among MS patients (Riise et al., 2003), and surveillance of MS by MRI and the ability to detect cancer in the brain and especially the meninges, at an early stage.

A possible explanation of why overall cancer risk is similar between MS patients and controls in the period from 1953 to 1995, and higher among MS patients compared to controls in the period 1996 to 2017, might be the older cohort and the ability to detect cancer among the elderly. Corroborating this assumption, we found that cancer diagnoses during 1996–2017 was more frequently observed among MS patients above 60 years of age. Since MS-patients are now living longer, this might also have led to an increased risk of cancer in this population (Lunde et al., 2017). In the follow-up period from 1953 to 1995, with similar incidence of cancer between MS patients and controls, we found significant higher age at cancer diagnosis among MS patients (42.5 years mean age) in comparison with controls (38.3 years mean age). Contrary, in the follow- up period from 1996 to 2017, we found significantly lower age at cancer diagnosis among MS patients (58.3 years mean age) compared to controls (59.7 years mean age). The period 1953 to 1995 revealed results on cancer incidence which are in concordance with previous studies on cancer incidence among MS patients, showing similar or lower incidence rates of cancer in MS (Norgaard et al., 2018, Hongell et al., 2019, Kingwell et al., 2012, D'Amico et al., 2019). Thus, the diversity in the age of the population and longevity on follow- up might explain the divergent results in cancer studies in MS until today.

In the period 1996 to 2017, we found a higher incidence of cancer among female MS patients in breasts, genitalia and digestive systems, compared to female controls. One possible mechanism could be that suppression of the immune system might result in women's susceptibility to human papilloma virus (HPV) and cervical cancers. These specific cancer types were not increased among MS patients during 1953 to 1995, in the era prior to DMT. MS patients who have developed breast cancer have been reported in clinical trials of interferons (Parker et al., 2016), natalizumab (Polman et al., 2006), fingolimod (Cuvillier, 2008), teriflunomide (Huang et al., 2015), alemtuzumab (Coles et al., 2017)and cervical cancer has been observed among patients treated with natalizumab (Polman et al., 2006), teriflunomide (O'Connor et al., 2011) and cladribine (Giovannoni et al., 2010). Gastric tumors have been observed among MS patients treated with fingolimod (Cuvillier, 2008) and hematological cancers have been observed among patients treated with natalizumab (Mori et al., 2004) (myeloma), fingolimod (Cuvillier, 2008) (lymphoma), cladribine (leukemia, lymphomas) (Lee et al., 2013) and alemtuzumab (Demko et al., 2008) (leukemia, lymphomas). These medications and possible cancer risks have recently been reviewed (Melamed and Lee, 2019). Our observation of these cancer types being significantly increased among MS patients in the era of DMT compared to previous periods points to a possibility that these drugs might play a role in higher cancer incidence among MS patients compared to the general population. However, surveillance might also overestimate cancer incidence among MS- patients due to MRI being part of the MS-follow, in genitals and urinary tract as examinations after MS related issues with miction/ defecation, and hematological cancers as result of MS patients' regular blood tests measuring white-blood-cells counts. Finally, multiple comparisons were not adjusted when estimating the subgroup cancer risks and these results should therefore be interpreted with caution.

Although the survival of in MS has increased, MS patients have still on average a shorter lifetime expectancy compared to the general population in Norway, and cancer is a primary cause of death (Lunde et al., 2017). In order to further improve survival, clinical awareness of cancer risk among MS patients, in the form of cervical screening (Nosek and Howland, 1997) and cancer screening in general (Cheng et al., 2001) could be important.

Our study does not support a hypothesis of diagnostic neglect of cancer in explaining overall cancer incidence in MS. Diagnostic neglect and clinicians failing to identify tumors equally among MS patients and peers without MS, resulting in later diagnosis and initiative to treat MS patients suffering from cancer (Kingwell et al., 2012), cannot explain divergent cancer risk in this investigation. Contrary, in this longitudinal cohort study, we found increased cancer risk among MS patients overall, and specifically increased brain cancer, cancer in the meninges, and cervical cancer, suggesting that frequent clinical, biochemical and radiological monitoring might detect malignant disease, rather than diagnostic neglect. Particularly cancers in the brain and meninges during 1996–2017 could be explained by ascertainment bias and the frequent MR scans in MS follow- up, which increases the ability to clinically identify tumors at early stage. The explanation for our findings of increased cancer in particular and cervical, breast and brain cancer specifically, contrary to previous reports indicating diagnostic neglect (Kingwell et al., 2012) can possibly be explained by the quality and appropriateness of data sources. In our study, we used data from the Norwegian Cancer Registry, which registers all cancer cases in Norway, contrary to Administrative data that might be prone to sampling bias (Kingwell et al., 2012). In addition, the Norwegian health system universally covers all citizens, with full access to diagnostic, and treatment

facilities.

Although the overall incidence of cancer among MS patients is more frequent after 1996 in the era of DMT, we also found a higher frequency of urinary – and hematological cancers among male MS patients in the total follow-up period from 1953 to 2017. This continuity on cancer excess among male MS patients seems therefore to be independent of DMT use, and might be a result of the MS-disease itself or common etiological risk factors.

Advantages of this study is the longitudinal registry based data with valid and reliable data from prevalence studies and population based registries. This cohort of patients were collected on a more structured way than medical records and administrative data collected for administrative purposes, rather than research. The cohort has been validated in previous studies (Bjornevik et al., 2017, Torkildsen et al., 2014) on MS risk factors. The Norwegian Cancer registry is an almost complete database (Larsen et al., 2009), the diagnostic accuracy is reliable and registration of cancer incidence is mandatory since 1953 to all clinicians in Norway. Adjustment for education as socioeconomic factor was made to adjust for MS outcome such as the variation of access to and compliance with health care utilization (Hillert, 2020) and risk of cancer. We also analyzed MS patients risk compared to individual matched controls on sex, age and county of residence. Thus, as age is a strong confounder of cancer risk we also adjusted the analyses for age in 1996, in order to prevent bias concerning MS patients' early death. The longitudinal design allowed for long-term observation of total cancer and types of cancer, which is to our knowledge a rarity among cancer studies in MS.

The main limitation of our study is the lack of data on DMT use. Thus, we are not able to verify if the increased cancer incidence during the last decades is caused by individual DMT use. Further, we do not have data to determine if some of the DMTs are associated with increased cancer risk compared to others. In the analyses we adjusted for education as a proxy for socioeconomic status shown to be important in assessment of MS outcome (Hillert, 2020). The main limitation regarding this adjustment was that we did not have individual behavioral data of life style risk factors for cancer, such as smoking, BMI and nutrition.

5. Conclusion

We found significantly increased overall cancer risk among MS patients during 1996 to 2017, in the era of introduction of DMT in Norway. Particularly, cancer in the brain, meninges and respiratory organs was increased for both female and male MS patients. This increased frequency of cancer diagnosis in the brain and meninges could be due to improved ascertainment on MR-screenings. Because of improved survival and longer life expectancy, MS patients are more susceptible to cancer diagnosis, and clinicians should be aware of the increased risk of cancer among MS patients above 60 years of age. To determine the role of long-term use of specific DMT in cancer risk, further longitudinal data is necessary.

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CRediT authorship contribution statement

Nina Grytten: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Kjell-Morten Myhr:** Conceptualization, Writing – review & editing, Funding acquisition. **Elisabeth G. Celius:** Data curation, Writing – review & editing. **Espen Benjaminsen:** Data curation, Writing – review & editing. **Margitta T. Kampman:** Data curation, Writing – review & editing. **Rune Midgard:** Data curation, Writing – review & editing. **Anita Vatne:** Data curation, Writing – review & editing. **Jan H. Aarseth:** Data curation, Writing – review & editing. **Trond Riise:** Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation, Writing – review & editing. **Øivind Torkildsen:** Conceptualization, Validation, Investigation, Writing – review & editing, Supervision, Funding acquisition.

Declaration of Competing Interest

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