Multiple Sclerosis and Related Disorders 35 (2019) 221–227

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Clinical trial

Risk of cancer among Finnish multiple sclerosis patients

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ARTICLE INFO

Keywords:
Multiple sclerosis
Breast cancer
DMT
Cohort study

Glossary: MS, multiple sclerosis
RRMS, relapsing remitting MS
SPMS, secondary progressive MS
PPMS, primary progressive MS
CNS, central nervous system
DMT, disease modifying treatment
ICD, International Classification of Diseases
IS, immunosuppressant
IFN, interferon
GA, glatiramer acetate
TFR, teriflunomide
DMF, dimethyl fumarate
OR, odds ratio
CI, confidence interval
BC, breast cancer
MRI, magnetic resonance image
EBV, Epstein-Barr virus
HL, Hodgkin lymphoma
BMI, body mass index

ABSTRACT

Background: Most studies that have investigated the association between multiple sclerosis (MS) and cancer have suggested a reduced overall cancer risk and no effect of long-term exposure to the immunomodulatory disease modifying treatments (DMTs). Some studies have suggested an increased cancer risk among MS patients treated with immunosuppressive (IS) therapies. Cancer risk among Finnish MS patients has previously been studied from an incidence cohort from 1964 to 1993 followed until year 1999. The objective of this nested case-control study was to assess the cancer risk among Finnish MS patients in a hospital district cohort from southwest Finland during the DMT era.

Methods: Patients with MS and cancer comorbidity were identified from the hospital administrative data at the Hospital District of Southwest Finland during a period from 1.1.2004 to 31.12.2012. Case ascertainment for MS diagnosis by the McDonald criteria was performed by review of medical records. During the follow-up 1074 confirmed MS cases were treated in the hospital district, including the deceased cases after 1.1.2004 (5.9%, $n = 70$). The randomly chosen 10-fold control population was matched by birth year and gender to calculate the coincident risks (odds ratio, OR) with 95% confidence intervals (95% CI) for each cancer diagnosis. Another separate control population from the same patient pool was used to verify the stability of the results. The Kaplan-Meier analysis and ANOVA test log rank test was applied to study cumulative index proportion and age (years) at breast cancer diagnosis in the MS and in the control group.

Results: A total of 61 (5,7%) of the MS patients and 757 (7,0%) of the controls were diagnosed with cancer during the study period. The overall risk of cancer in the MS cohort did not significantly differ form the controls (OR 0.80, 95% CI 0.6–1.0, $p = 0.092$). The age at breast cancer diagnosis in the MS cohort was statistically significantly higher in comparison to the control cohort (61,7 vs. 55.7 years, ANOVA test p-value 0.010). However, the risk for breast cancer did not statistically significantly differ between MS patients and controls (OR 0.9, 95% CI 0.5–1.4, p-value 0.566). In the MS cohort we observed an increased risk of oral cavity cancers (OR 10, CI 1.1–94.2, p-value 0.04), colon cancer (OR 2.3, 95% CI 1.1–5.2, p-value 0.037), lung cancer (OR 4.4, CI 1.5–13.0, p-value 0.007), renal cancer (OR 3.6, CI 1.2–10.6, p-value 0.018), brain cancer (OR 5, 95% CI 1.1–23.0, p-value 0.039) and thyroid cancer (OR 3.6, 95% CI 1.2–10.6, p-value 0.018), and a decreased risk for prostate cancer (OR 0.2, 95% CI 0.1–0.8, p-value 0.026), although for these cancer subtypes the patient numbers were small.

Conclusions: Overall risk of cancer in our MS cohort did not significantly differ from the controls. However, the age at diagnosis of breast cancer was statistically significantly higher among the MS patients in comparison with a control population from the same patient pool. Further population-based larger studies spanning longer follow-up periods and longer exposure to emerging MS therapies are needed to evaluate cancer risk related to MS treatments and breast cancer risk in particular.

1. Introduction

Multiple sclerosis (MS) is the most common chronic immune-mediated demyelinating disease of the central nervous system (CNS) and a leading cause of non-traumatic neurological disability in young adults. MS prevalence varies considerably worldwide, with an overall

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https://doi.org/10.1016/j.msard.2019.08.005
Received 18 April 2019; Received in revised form 29 July 2019; Accepted 4 August 2019

higher prevalence in women (Moroni et al., 2012; Rosati, 2001). Finland is a high-risk region of MS with large regional epidemiological differences (Holmberg et al., 2013; Krökki et al., 2011; Sarasoja et al., 2004; Sumelahti et al., 2001 and 2003). The incidence and prevalence of MS and the age of the MS population are increasing globally (Magyari and Soelberg-Sorensen, 2019). We have recently updated the prevalence and incidence of MS in southwest Finland. Age-standardized prevalence to European standard population was 280/100 000 and incidence 12.1/100 000, which are among the highest in Finland and globally very high (Pirttisalo et al., 2018a). Female-to male ratio in western Finland has increased from 2.2 to 2.7 since 1990ies and the mean age of the MS population has increased in the same time from less than 40 years to over 50 years (Sumelahti et al., 2003; Pirttisalo et al., 2018a). In the aging population with MS comorbidities such as cancer play a growing role. In Finland, a total of 250 000 people had cancer at some point in their lives in the year 2011 and there were 30 000 new diagnosed cancer cases. Cancer becomes more common with increasing age and the annual number of cancer deaths among Finns has remained stable around 11 700, with pulmonary cancer as the most common cause of cancer death. The most common cancer in women is breast cancer (BC, $n = 4900$) and in men prostate cancer ($n = 4700$) (Pukkala and Rautalahti, 2013; The Finnish Cancer Registry, www.cancerregistry.fi).

The immune system plays an important role both in MS and cancer, making it plausible that cancer risk is altered in MS. Studies of cancer risk in MS patients have, however, been inconsistent (Capkun et al., 2015; Kingwell et al., 2012; Kyritsis et al., 2015; Marrie et al., 2015; Roshanisefat et al., 2015; Tabarés-Seisdedos and Rubenstein, 2013; Thormann et al., 2016).

Most studies have suggested a reduced overall risk for cancer among MS patients and no effect of long-term exposure to the immunomodulatory (IM) disease modifying treatments (DMTs) glatiramer acetate (GA) and interferons (IFN) (Gaindh et al., 2016). Some studies suggest a possible association of DMTs and increased BC risk (Aschiron et al., 2005; Kingwell et al., 2014). Several reports suggest an increase in cancer risk among MS patients treated with traditional immunosuppressive (IS) therapies such as azathioprine, cyclophosphamide and mitoxantrone (Achiron et al., 2005; Le Bouc et al., 2012; Kingwell et al., 2014; Lebrun et al., 2008 and 2011; Ragonese et al., 2017).

Because of their action on the immune system, and due to a lack of available long-term data, a special warning of the potential risk of cancer accompanies the use of recent IS such as cladribine, fingolimod, natalizumab, alemtuzumab, ocrelizumab, and possibly dimethyl fumarate (DMF) and teriflunomide (TRF) (Ajdadic-Gross et al., 2016; Bar-Or, 2008; Clerico et al., 2017; Coles et al., 2017; Comi et al., 2017; D´Amico et al., 2018; Giovannoni, 2017; Hauser et al., 2017; Havrdova et al., 2017; Lebrun and Rocher, 2018; McGinley et al., 2017; Montalban et al., 2017; Sabol et al., 2017; Tully et al., 2015).

Smoking is a known risk factor for MS, progression of the disease and of many cancers (Ramajunam et al., 2015). Epstein-Barr virus (EBV) is more common among MS patients than the population in general and seems to play a fundamental role in the pathogenesis of both autoimmunity (i.e. MS) and possibly in cancers, such as nasopharyngeal cancer, lymphoproliferative disorders, smooth muscle tumors, gastric carcinoma, Hodgkin-lymphoma (HL) and less clearly in BC (Anagnostouli et al., 2014; Khankanian et al., 2016; Levin et al., 2010). Studies on the prevalence of smoking among MS patients compared to the population in general have for a long time been scarce, despite the fact that smoking is an identified risk factor for disease onset and burden. In a study from 2006 the prevalence of smoking was not higher among MS patients than controls in the USA, whereas other and more recent studies have reported higher prevalence of smoking among MS patients when compared to the general population in Sweden, USA and Norway (Fiend et al., 2006; Hedström et al., 2009 and 2015; Nortvedt et al., 2005; Turner et al., 2007). We found no studies that have assessed the prevalence of smoking among Finnish multiple sclerosis patients compared to the Finnish population in general.

Cancer risk among Finnish MS patients has previously been studied from an incidence cohort from 1964 to 1993 followed until year 1999. In a cohort of 1597 MS patients, 85 cancers were identified. A small increased risk of hematological malignancies and CNS tumors was observed, but no association of overall cancer and MS (Sumelahti et al., 2004).

IFNs became available in Finland in the mid 1990s, GA since 2004, natalizumab 2006, fingolimod 2011, alemtuzumab and TFR 2013 and DMF in 2014. In a previous study we showed that the proportion of infections among hospital admissions of MS patients in Finland has increased during the past decade (Pirttisalo et al., 2018b). There are no previous studies assessing the risk of cancer among Finnish MS patients in the era of MS therapies. The objective of this study was to assess the risk of cancers among MS patients in a prevalence cohort from a large hospital district in southwest Finland from year 2004 to 2012.

2. Materials and methods

2.1. Patients and methods

The study has been performed in accordance with the code of ethics of the World Medical Association, i.e. ethical standards laid down in the 1964 Declaration of Helsinki and it´s later amendments. The study was registered and approved by the Turku Clinical Research Center and ethical committee approval was obtained from the joint Ethics Committee of the Tampere University and Pirkanmaa Hospital District.

Patients with ICD-9 (3400A) and ICD-10 (G35) codes for MS were searched for from the hospital administrative data in the hospital district of southwest Finland from January 1, 2004 to December 31, 2012, as described previously (Åivo et al., 2017; Murtonen et al., 2018). The deceased cases ($n = 70$) after 1.1.2004 were inluded. Cancers in the MS cohort and control group were searched for by ICD-10 codes C00-C96. Cancers diagnosed both before and after the date of definite MS diagnosis were included ($n = 1074$). The control population was a 10-fold population ($n = 10740$) with the same gender and year of birth, randomly selected from the Turku University Hospital patients register. Another separate control population from the same patient pool was used to verify the stability of the results. ORs and 95% CIs were calculated for the overall risk of cancer and for the risk of specific cancer types in the cohorts. Patient documents of the confirmed MS cases with diagnoses of cancers were reviewed by K.H. to assess disease type, smoking habits, alcohol use, profession, use of vitamin-D supplements, BMI, parity, family history of cancers and MS, first symptom of MS, first symptom or sign of cancer, received cancer treatments (surgery, radiation and chemotherapy), other surgery, Expanded Disability Status Scale (EDSS), the use of MS therapies, use of other medications including hormonal replacement therapies, type of cancer or cancers and the outcome of cancer. The causes of all deaths during the study period were obtained by the review of the patients charts (M-L S) as described previously (Murtonen et al., 2018).

2.2. Statistical analysis

The ORs were calculated with 95% CIs and p-values were calculated using Pearson's χ^2 test. Age at BC diagnosis was compared between groups using ANOVA test. All statistical tests were two-tailed and p-values less than 0.05 were considered statistically significant. Statistical analyses were performed using R Statistics version 3.0.2 with standard packages.

Kaplan-Meier (KM) analysis was performed for cumulative incidence proportion and age (years) at BC diagnosis for MS and year of birth- and gender matched controls. Significance was assessed by log-rank test.

3. Results

During the follow-up from 1.1.2004 to 31.12.2012, a total of 1074 confirmed MS cases were treated in the hospital district, including the 70 deceased cases after 1.1.2004 (5.9%). The gender distribution in our MS cohort of 1074 patients was 759 females (70.7%) and 315 males (29.3%). The control population was 10-fold and matched for year of birth- and gender distribution. Another separate year of birth- and gender-matched 10-fold control population from the same patient pool was used to verify the stability of the results in the district without deviations. A total of 818 patients in the summoned MS and control cohorts were diagnosed with cancer (mean age 58.8 years, SD 12.16). A total number of 68 cancer diagnoses were found in the MS cohort, and after adjusting for multiple cancers in part of the individuals, a number of 61 MS patients with cancer comorbidity were identified (5.7%, mean age 57.3 years, SD 13.15) and 757 controls with cancer comorbidity (7.0%, mean age 58.9 years, SD 12.08) (ANOVA p-value 0.317). Among the 70 MS patients that deceased during the study period, there were a total of 11 cases of cancer (5 cases of BC, 3 intestinal cancers, 2 pulmonary cancers and 1 thyroid cancer). Only in 3 of these cases, cancer was the cause of death (2 cases of BC and 1 intestinal cancer) during the study period among the MS patients (4.3% of all causes of deaths among the MS-patients). Other causes of death among the deceased MS patients were two cases of respiratory infection, two unlocalized infections and four cases of respiratory insufficience.

In the MS cohort, the risks for oral cavity cancers, colon cancer, lung cancer, renal cancer, brain cancer and thyroid cancer (ICD-codes C04&C06, C18, C34, C64, C71 and C73) were increased, and decreased for prostate cancer (C61), although the patient numbers were too small to draw any conclusions of statistical significance. There was a slight trend towards a decreased risk for BC among MS patients when compared to controls (OR 0.9, 95% CI 0.5–1.4) (Table 1). Among the patients with BC ($n = 225$), all of which were female, a statistically significantly higher age at cancer diagnosis was observed in the MS cohort ($n = 18$) in comparison to the control pool ($n = 207$) (61,7 years and SD 10.5 vs 55,7 years and SD 9.2. For the total of 225 BC cases, mean age was 56,2 years and SD 9.4 (ANOVA p-value 0.010) (Fig. 1A and B).

Within the cohort of MS patients diagnosed with BC ($n = 18$), 7 had no DMT and 5 had received DMT (IFN, of which three patients switched to GA), for 6 data was not available. 3 BC patients in the MS cohort had PPMS, and 1 PPMS patient had received several intravenous methylprednisolone pulse treatments. Among the MS patients with BC, only one patient (5.6%) had a known history of smoking and eight patients (44.4%) were self-reported non-smokers. For the remaining patients (50%) data of smoking history was not available. Alcohol consumption was negative ($n = 2$), low ($n = 4$) or not available ($n = 12$). Five of the women had given birth twice, two patients had a history of one or two abortions and data on the remaining patients was not available. Six BC cases were diagnosed by routine age group screening and three BC patients had received hormonal replacement therapies (topical estrogens). Data on vitamin D supplement use was available only for one BC patient.

MS patients diagnosed with cancers that showed an increased risk (ICD-codes C04&C06, C18, C34, C64, C71 and C73) in our cohort had been treated with IFN, GA, intravenous methylprednisolone cortisone pulses, and natalizumab. One of the patients participated in a study and had received either TRF or placebo. There was only one MS patient who had received natalizumab. The patient had an unknown smoking status and was diagnosed with lung cancer. Data on smoking status, alcohol consumption, parity, BMI, socioeconomic status/profession, EDSS, family history of MS and cancer, hormone replacement therapy and vitamin D supplement use was scarce in the medical records. One MS patient with brain cancer had a known family history of cancers. For the rest of the patients, data on family history of cancer was not available.

Other types of cancers were represented in small patient numbers and without statistically significant increased or decreased risk of occurrence in the MS cohort as shown in Table 1. Cancers only observed in the control population, but not in the MS cohort, are not listed in the table or described further in detail in the manuscript.

Table 1
Odds ratios (OR) and 95% confidence intervals (CI) of cancers in MS patients in comparison to year of birth- and sex- matched controls.

ICD-10 code	cancer type	MS N (%)	Control N (%)	OR	CI (95%)	p-value
C02	tongue cancer	1 (0.1)	8 (0.1)	1.3	0.2 – 9.9	0.833
C04	**cancer of floor of mouth**	**1 (0.1)**	**1 (0.0)**	**10.0**	**1.1 – 94.2**	**0.044**
C06	**cancer in other mouth parts**	**1 (0.1)**	**1 (0.0)**	**10.0**	**1.1 – 94.2**	**0.044**
C18	**colon cancer**	**7 (0.7)**	**30 (0.3)**	**2.3**	**1.1 – 5.2**	**0.037**
C25	pancreas cancer	1 (0.1)	5 (0.0)	2.0	0.2 – 16.4	0.519
C34	**lung cancer**	**4 (0.4)**	**9 (0.1)**	**4.4**	**1.5 – 13.0**	**0.007**
C43	melanoma	2 (0.2)	30 (0.3)	0.7	0.2 – 2.8	0.576
C44	other skin malignancies	5 (0.5)	87 (0.8)	0.6	0.2 – 1.4	0.221
C49	connective tissue cancer	1 (0.1)	9 (0.1)	1.1	0.1 – 8.8	0.920
C50	breast cancer	18 (1.7)	207 (1.9)	0.9	0.5 – 1.4	0.566
C53	cervix cancer	1 (0.1)	5 (0.0)	2.0	0.2 – 16.4	0.519
C54	uterus cancer	1 (0.1)	30 (0.3)	0.3	0.1 – 2.2	0.255
C56	ovarian cancer	2 (0.2)	29 (0.3)	0.7	0.2 – 2.9	0.609
C61	**prostate cancer**	**2 (0.2)**	**86 (0.8)**	**0.2**	**0.1 – 0.8**	**0.026**
C64	**renal cancer**	**4 (0.4)**	**11 (0.1)**	**3.6**	**1.2 – 10.6**	**0.018**
C67	bladder cancer	3 (0.3)	16 (0.16)	1.9	0.6 – 6.3	0.309
C71	**brain cancer**	**2 (0.2)**	**4 (0.0)**	**5.0**	**1.1 – 23.0**	**0.039**
C72	other CNS cancer	1 (0.1)	3 (0.0)	3.3	0.4 – 28.1	0.268
C73	**thyroid cancer**	**4 (0.4)**	**11 (0.1)**	**3.6**	**1.2 – 10.6**	**0.018**
C74	adrenal cancer	1 (0.1)	2 (0.0)	5.0	0.6 – 43.3	0.144
C79	metastasis in other location	2 (0.2)	8 (0.1)	2.5	0.6 – 11.2	0.230
C81	Hodgkin disease	1 (0.1)	2 (0.0)	5	0.6 – 43.3	0.144
C83	diffuse non-Hodgkin lymphoma	2 (0.2)	14 (0.1)	1.4	0.3 – 6.2	0.635
C91	lymphatic leukemia	1 (0.1)	12 (0.1)	0.8	0.1 – 6.4	0.861

MS-patients $n = 1074$, controls = 10740. Numbers in the table represent cancer diagnoses, not the number of MS and control cases diagnosed with cancers. In both cohorts, patients with multiple cancer diagnoses were observed, resulting in different numbers of cancer diagnoses and number of cases with cancer. Cancers observed in the control cohort, but not in the MS cohort, were excluded from this table. P-value was obtained from a two-tailed t-test and values less than 0.05 were considered statistically significant. N = number of patients with a cancer diagnosis, OR = odds ratio, CI = confidence interval.

The age at cancer diagnosis did not statistically differ between MS patients and controls (Table 2), except for BC where mean age at diagnosis was statistically significantly higher among MS patients compared to controls (61.7 years and SD 10.5 vs. 55.7 years and SD 9.2, ANOVA p-value 0.010) (Fig. 1A and B). A Kaplan-Meier curve of cumulative incidence proportion and age (years) at BC diagnosis in MS patients and controls is shown in Fig. 1A.

4. Discussion

We performed a nested case-control study assessing the cancer risk in a cohort of over 1000 MS-patients followed for a period from 2001 to 2013 (approximately 9000 patient years) in a University Hospital District in Southwest Finland. Similar to the previous study from Finland (Sumelahti et al., 2004), we did not find a difference in the overall risk of cancer among Finnish MS patients. The comparison was made with a randomly selected 10-fold sex- and year of birth- matched control group from the same population pool. The risk of the most common cancer type among the studied population, BC, did not significantly differ between the MS patients and the controls. However, the age at BC diagnosis was 6 years higher in the MS cohort compared to

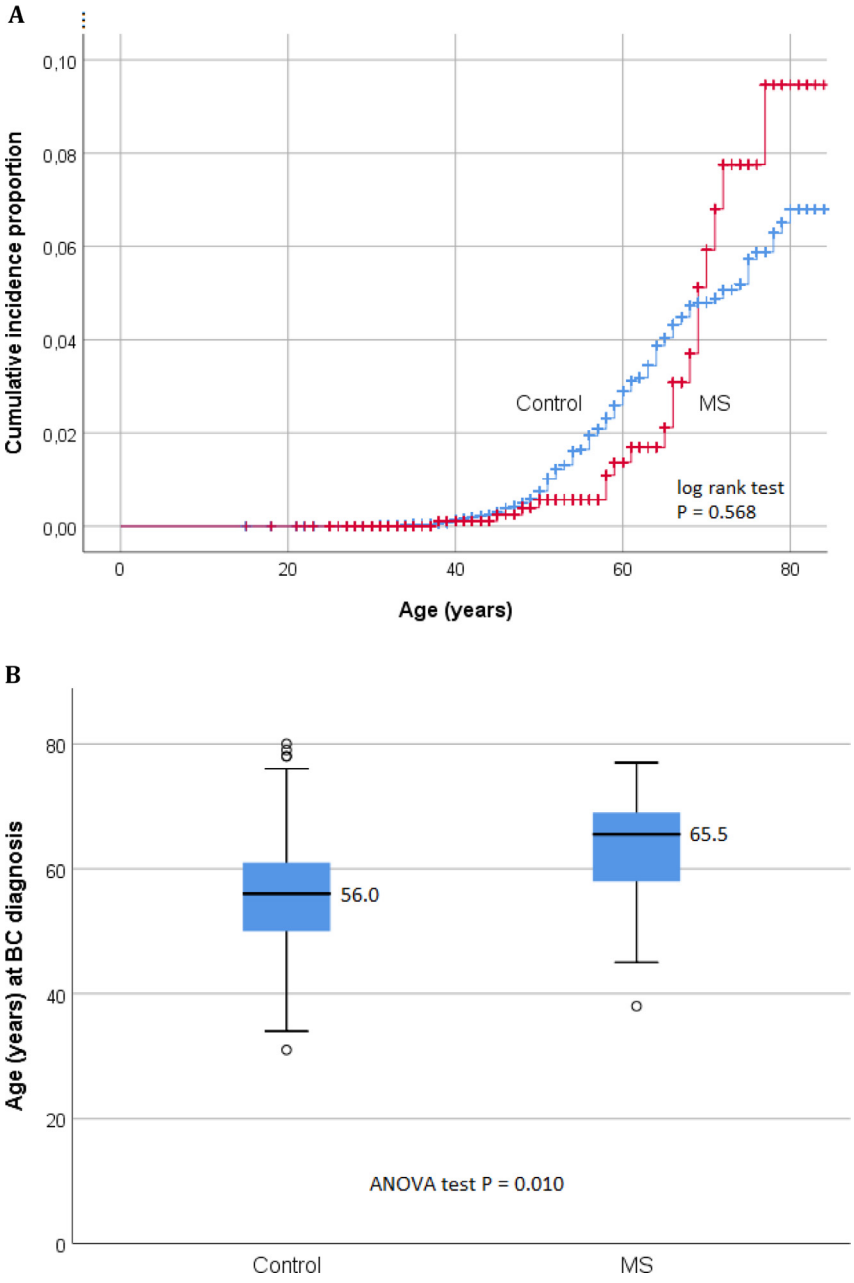

Fig. 1. (A) Kaplan-Meier curve of cumulative incidence proportion and age (years) at breast cancer (BC) diagnosis in MS (red print) and year of birth- and gender-matched controls (blue print) (N tot 225). MS cases were enrolled from 1.1.2004 to 31.12.2012 in the Hospital District of Southwest Finland. A statistically significantly higher age at BC diagnosis was observed in the MS patients (n = 18) in comparison to controls (n = 207) (mean age 61,7 years and SD 10.5 vs. 55,7 years and SD 9.2, ANOVA test p-value 0.010, log rank test p-value 0.568 by a two-tailed t-test), whereas overall risk of BC cancer was similar in the two groups. Notice that the y-axis is cut off at 0.10. N tot = total number of BC patients; N tot = total number of BC patients; BC = breast cancer. (B) Age (years) at breast cancer (BC) diagnosis in MS and year of birth- and gender-matched controls (N tot 225). MS cases were enrolled from 1.1.2004 to 31.12.2012 in the Hospital District of Southwest Finland. A statistically significantly higher age at BC diagnosis was observed in the MS patients (n = 18) in comparison to controls (n = 207) (mean age 61,7 years and SD 10.5 vs. 55,7 years and SD 9.2, ANOVA test p-value 0.010), whereas overall risk of BC cancer was similar in the two groups. BC = breast cancer; N tot = total number of patients with BC.

Table 2
Age (years) at cancer diagnosis among MS patients and the year of birth- and sex-matched controls.

Group	Mean	SD	N	
Control	58,92	12.08	757	
MS	57,30	13.15	61	
Total	58,80	12.16	818	p = 0.317

N = number of patients, SD = standard deviation. P-value was obtained from a two-tailed t-test and values less than 0.05 were considered statistically significant.

the control group. Trends were observed for increased risks of brain cancer, renal cancer, oral cavity cancer, lung cancer, colon cancer and thyroid cancer, and a decreased risk for prostate cancer among the MS patients. The risks for other cancer types did not show any difference in comparison with the controls.

In addition to previous conflicting results in studies regarding the overall risk of cancer in MS, study findings on the risk of specific cancer types have also been inconsistent. This may be due to differences in study design and methods of case ascertainment, as well as diagnostic neglect or disease associated characteristics or exposures (Boussios et al., 2015; Krhut et al., 2014; Kyritsis et al., 2015; Marrie et al., 2015; Sun et al., 2014; Kingwell et al., 2012). There is some evidence for an increased risk for HL in MS patients. HL is a disease that, in addition to sharing environmental risk factors with MS, such as Epstein-Barr virus (EBV) infection and exposure to ultra violet (UV) light, is also genetically related to MS (Khankanian et al., 2016).

Overweight, smoking and low parity are risk factors linked to both BC and MS in previous studies. Compelling endocrinological and genetic evidence strongly link BC and MS, but conclusive epidemiological answer to whether MS increases or decreases risk for BC is lacking (Holzmann et al., 2013; Huang et al., 2015; O´Malley et al., 2015; Sun et al., 2014).

On the other hand, there are studies suggesting a possible potential of anticancer activity of TRF on aggressive subtype triple-negative

breast cancer (TNBC) and non-small cell lung cancer (NSCLC) (Huang et al., 2015; Jiang et al., 2018).

In a recent Swedish population-based cohort study on BC risk among pre- and postmenopausal MS patients, no association between MS (diagnosed between 1968 and 2012) and premenopausal or overall BC risk was observed (Hajiebrahimi M et al., 2016). There was, however, a slightly elevated risk of postmenopausal BC among the MS patients that were diagnosed with MS between 1968 and 1980 and at a higher age (>65 years). The finding was speculated to be due to bias from a more prompt surveillance due to MS monitoring or associated to lower parity among MS patients compared to controls. Another recently published study from Denmark reported that women with MS did not have increased risk of BC or overall cancer compared to the general population (Nørgaard et al., 2018). In a previous cohort of 5146 MS patients from British Columbia followed for almost 50000 patient years, there was a non-significant trend towards an increased risk of IFNβ exposure in the BC cases (Kingwell et al., 2014). There were no differences in the tumor size of BC between the IFNβ treated and untreated cases or any indication of a dose-response effect. The reason why BC may have emerged as possibly associated with IFN in the study is unclear, but absence of a dose-response effect might argue against a true association. The study found no sign of a lead time bias or evidence to suggest that treated patients were monitored more carefully for cancer, as the tumor size distribution at the time of cancer diagnosis was comparable for IFN and non-exposed cancer cases. However, the possibility that the potential effects of a more vigilant monitoring of treated patients and an enhancement of tumor growth of IFN could cancel each other out could not be ruled out (Kingwell et al., 2014). In their previous publication on a cohort study from British Columbia, the authors found a decreased risk of overall cancers among MS patients. The study was not designed to address the impact of DMTs or IS on cancer risk, but sensitivity analysis revealed that the estimates were no different for the treatment naïve cohort. BC tumors were larger among the MS patients compared to the control cohort, suggestive of a later stage at diagnosis and possibly implicating diagnostic neglect (Kingwell et al., 2012).

In our single center cohort of over 1000 MS-patients and 9000 patient years of follow-up, we observed a statistically non-significant inversed association between BC and MS. Five of the 18 MS-patients with BC had used IFN and/or GA. Our results do not support an increased risk of BC after exposure to IFN. The statistically significantly higher age at BC diagnosis among MS patients compared to controls observed in our study could speculatively be linked to a protective effect of a more active immune system in the MS patients. An alternative explanation is a negative surveillance bias caused by neglect of the patient's other symptoms and complaints than the MS related ones, or reluctance of the patients to attend the screening mammography in addition to the follow-up burden caused by frequent MS clinic visits. The difference in the age at diagnosis was as long as six years making the latter explanation maybe less likely. The higher age at BC diagnosis among MS patients could indicate diagnostic neglect, but there was no data on the BC tumor size at diagnosis to support this speculation.

In the Finnish population, the habit of daily smoking among adults (age 20–64 years) has decreased since 1997 and was 15% among men and 12% among women in the year 2017. From year 2004 to 2012 the amount of daily smoking females (age 20–64 years) decreased from 19% to 13%. The amount of daily female smokers in the elder population (age 65–84 years) remained mainly an unchanged 5% from year 2003 to 2012 (THL Tobacco Statistics, 2017).

In our cohort of MS patients diagnosed with BC ($n = 18$) 44,5% were non-smokers and for 50% smoking history was not available. Smoking habits among BC patients in our cohort (5,6%) were not lower when compared to the smoking elder Finnish female population (5%) in general, but the percentage was lower than for smoking Finnish females aged 20–64 years (13%). The reported low rate of smoking among our MS patients with BC could possibly have an impact on the slightly lower rate of BC among these MS patients and a possibly later onset of BC when compared to the controls and the Finnish population in general.

We found trends of increased risk for brain cancer, oral cavity cancer, renal cancer, lung cancer, colon cancer and thyroid cancer, and a trend of decreased risk for prostate cancer. In the majority of cancer cases in our MS cohort, cancer diagnosis was preceded by the MS diagnosis. This is in line with the known fact that MS is predominantly a disease of young adults, whereas the risk of cancer occurrence increases over time. On the other hand, studies from the era before IS and DMTs have linked MS to a reduced risk of overall cancer, and later study findings of increased cancer risk among MS patients might imply a role of MS therapeutics in predisposing to cancers. The decreased risk of prostate cancer among MS patients in our study is in line with a majority of previous study evidence (Kyritsis et al., 2015). The increased risk of brain cancer in our study is in line with some previous studies and may reflect a surveillance bias from a more frequent routine magnetic resonance image screening of MS patients (Kingwell et al., 2012). A small excess of brain cancer was similarly observed in the earlier study concerning cancer risk of MS patients in Finland (Sumelahti et al., 2004). The increased risk of renal cancer and colon cancer in our MS cohort might reflect a more common referral policy to urologists for evaluation of MS related symptoms as well as for gastroenterologist evaluation of bowel dysfunction. MS follow-up routine in the clinic might in this way lead to a more prompt diagnosis of these comorbidities and yield an added benefit to the patients. Increased risk for oral cavity cancer and lung cancer as well as thyroid cancer could reflect a shared risk factor for MS and cancer such as smoking, or possibly reflect a more frequent routine of X-ray imaging related to disease exacerbations and screening for underlying infections. Among the small number of MS patients diagnosed with brain cancer, renal cancer, lung cancer and oral cancer in our cohort we found that 40% were smokers, 30% non-smokers and for 30% data was not available. Unfortunately, the smoking history of all MS patients and controls was not available, preventing us from drawing any conclusions of the impact of smoking on cancer risk among the MS patients and in comparison with the controls. However, the percentage of smokers among MS patients in our cohort diagnosed with brain cancer, lung cancer, renal cancer and oral cancer, was higher than the percentage smokers in the Finnish population in general. It could be speculated that smoking (rather than MS itself) had an impact on the increased rates of these cancer subtypes in our study.

Previous conflicting study findings of MS and cancer comorbidity risk or association of these diseases might reflect the variability of different populations, time of analysis and variability in the MS pharmacotherapies used. None of the MS patients in our cohort had used mitoxantrone, which bears the well-known risk of treatment-related acute leukemia (Ellis et al., 2015). The MS patients in our cohort had mostly used platform MS therapies and IS treatments had been used only in one MS case with lung cancer (natalizumab from January 2010 to March 2012). BC patients in our cohort received only IFN and/or GA, but the patient numbers were small and no conclusion on the possible impact of DMTs on cancer risk in our cohort could be made.

During the past few years several new MS therapeutics have emerged. In the ocrelizumab phase III studies, an equal or increased risk of BC among the relapsing MS population and a signal for an increased risk of BC among the PPMS population were observed (Montalban et al., 2017; Hauser et al., 2017). In case the trend of a lower baseline risk for BC in MS patients compared to non-MS patients is accurate, then even an equal risk for BC among ocrelizumab-treated patients, when compared to IFN or placebo, could suggest that there is an increased BC risk associated with ocrelizumab exposure. Our study did not confirm this hypothesis and longer follow-up studies are needed to evaluate cancer risk related to MS treatments and BC risk in particular.

Our MS cohort was reasonably large, representing about 15% of the total MS population in Finland, but for the detection of rare and slowly developing diseases such as cancers, large population based studies

spanning decades of follow-up are necessary. The number of cancer patients in the MS cohort was relatively small ($n = 61$), and the subgroups of specific cancers even smaller, making statistical conclusions regarding the more rare cancers uncertain. Data on ethnicity was not available in our study cohort, but the population in southwest Finland consists of mainly Caucasian patients. The study findings may thence not apply to other ethnicities and geographical areas. The results in our study are not confounded by complicated histories of different DMTs, but the numbers of patients treated with specific DMT profiles in the cancer cohort were too small to make any conclusions of DMT impact on cancer risk possible. Another caveat of our study is the scarce information on possible confounding factors that may alter the risk of both MS and cancer, such as parity, smoking, vitamin D status, hormonal replacement therapy and other medications, alcohol use, BMI, family history and socioeconomic status.

5. Conclusion

Overall risk of cancer in our MS cohort did not significantly differ from the controls. However, we observed a statistically significantly higher age at BC diagnosis among the MS patients in comparison with a randomly chosen 10-fold year of birth- and sex-matched control population from the same patient pool. There was a trend towards a slightly lower BC risk in the MS cohort. Further population-based studies spanning longer follow-up periods are needed to confirm the MS patient´s cancer risk during the era of evolving MS treatments.

Author contributions and declaration

The corresponding author contributed by study design, writing the first draft of the manuscript and together with Merja Soilu-Hänninen and Marja-Liisa Sumelahti, review of medical records. Merja Soilu-Hänninen and Marja-Liisa Sumelahti contributed by study design and writing the manuscript and Samu Kurki for biostatistician analysis and writing the manuscript. All authors have seen and approved the final version of the manuscript.

Study funding

The corresponding author got financial funding from the Maire Taponen Foundation, the Perklén Foundation and the Finnish Medical Foundation.

Ethical standards

The study has been performed in accordance with the code of ethics of the World Medical Association, i.e. ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The study was registered and approved by the Turku Clinical Research Center and ethical committee approval was obtained from the joint Ethics Committee of Tampere University and Pirkanmaa Hospital District.

Declaration of Competing Interest

The corresponding author has received travel grants and financial support for participation in international congresses by Novartis, Biogen Idec, and Teva. Merja Soilu-Hänninen has obtained lecture fees and travel reimbursements from Bayer, Biogen Idec Finland, Genzyme Merck, Novartis, Sanofi, Orion and Teva. Marja-Liisa Sumelahti and Samu Kurki declare no financial or other conflicts of interest.

Acknowledgements

MD Katariina Hänninen is acknowledged for case ascertainment of the MS diagnoses by review of medical records, and the Maire Taponen Foundation, the Perklén Foundation and the Finnish Medical Foundation for financial funding of the study.

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