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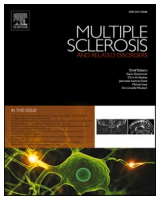

Original article

Cancer related mortality in multiple sclerosis. A population based cohort study

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ABSTRACT

Background: Cancer is a major cause of death, but how cancer influences mortality risk in Multiple Sclerosis (MS) is unclear.
Objectives: Determine all-cause mortality and mortality following a cancer diagnosis among MS patients compared with matched population controls.
Methods: Norwegian MS patients born 1930 - 1979 (n= 6950) followed-up 1953 – 2016, were matched with 37 922 controls. We compared incident cancer diagnosis from the Cancer Registry of Norway, date of death from the Cause of Death Registry, education from the National Education Database, by multivariate Cox proportional hazard regression.
Results: Hazard ratio (HR) and 95% confidence interval (CI) for all-cause mortality among MS patients was 4.97 (4.64 – 5.33), and 2.61 (2.29 – 2.98) for mortality following a cancer diagnosis. Mortality in MS was highest following urinary- (2.53: 1.55 – 4.14), colorectal- (2.14: 1.47 – 3.11), hematological- (1.76: 1.08 – 2.88), ovarian - 2.30 (1.73-3.06) and breast cancer diagnosis (2.61: 1.85 – 3.68), compared to controls. High education was inversely associated with mortality among MS patients.
Conclusions: All-cause mortality was five- fold and mortality following a cancer diagnosis was two- fold increased among MS patients. Mortality following specific cancers raises the possibility of diagnostic neglect.

1. Introduction

Patients with multiple sclerosis (MS) have reduced life expectancy, and cancer is one of the major causes of death (Lunde et al., 2017). The risk of developing MS is associated with adverse life style habits such as smoking (Riise et al., 2003) and obesity (Hoglund et al., 2021; Marrie et al., 2009a). MS is associated with comorbid diseases (Marrie et al., 2015; Marrie et al., 2009b) and lower education (Bjornevik et al., 2017) that might also impact the risk of cancer and early death. In addition, some MS disease modifying therapies (DMT) might influence the risk of cancer (Alping et al., 2020; Buttmann et al., 2016).

Previous studies have reported different results regarding the risk of death due to cancer among MS patients (Bronnum-Hansen et al., 2004; Grytten Torkildsen et al., 2008; Kingwell et al., 2020; Lalmohamed et al., 2012; Lunde et al., 2017; Marrie et al., 2021a; Norgaard et al., 2019; Roshanisefat et al., 2015; Smestad et al., 2009; Thormann et al., 2017). The conflicting results probably reflect methodological heterogeneity in these studies.

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We have previously reported an increased risk of cancer in central nervous system (CNS), and in urinary and respiratory organs, but a lower frequency of haematological cancers among MS-patients compared to the general population (Grytten et al., 2019). MS symptoms could mimic some of the early signs of breast- and colorectal cancer, and could thus theoretically lead to diagnostic delay and increased mortality (Kingwell et al., 2012). Therefore, these cancers, which are accounting for half of cancer deaths in the adult population (Cancer. 2022), were selected for further investigation of mortality.

The objective of this study was to determine all-cause mortality and the mortality following cancer diagnosis among Norwegian MS patients, compared with matched population controls.

2. Methods

2.1. Study populations

The Norwegian Multiple Sclerosis Registry (Myhr et al., 2015), established in 2001 was the primary source for identifying patients in this study. The study population was supplied by population-based epidemiological data on MS patients born between 1930 and 1979 in Norway, retrieved from previous studies as described before (Bjornevik et al., 2017; Grytten et al., 2013; Kampman et al., 2013). Additionally, we included data from about 1200 patients with MS in a cohort enrolled in the Oslo MS Registry (Celius and Smestad, 2009). The patients had been diagnosed with MS according to the criteria of Poser (Poser et al., 1983) or McDonald (Polman et al., 2005).

The Norwegian Population Registry (Statistics Norway) established in 1964, provides personal identification numbers for the total population of Norway. We individually matched MS patients with five controls provided by Statistics Norway, adjusted for the birth year, area of residence, and sex. We linked the complete cohort of cases (n=6950) and the matched population controls (n = 37,922), from Statistics Norway, to the Cancer Registry of Norway. All cancer cases have been mandatory registered in the Cancer Registry of Norway since 1953, and the quality of data is considered timely, close to complete by 98%, comparable and accurate (Larsen et al., 2009).

The Cancer Registry of Norway provided incidence data on diagnosis according to the International Classification of Diseases versions 7–10 (ICD-7–10). We retrieved the date of cancer diagnosis for all MS patients and population controls, who developed cancer until December 31, 2016. We also obtained data on attained educational level for all cases from the National Education Database, which records all individually based data on education, from completed lower secondary education to tertiary education. Level of education was included in the model as a proxy for socioeconomic status. The cohort was linked to the Cause of Death Registry, established in 1951, to obtain the date and the underlying causes of death according to death certificates.

The index date for linking patients and controls by county of residence was set to their 15th birthday. We chose this 15th birthday as index date because it was early in a possible preclinical course, while still being able to implement registered residence for the majority in the sample. Data on residence were not available before the 1960 census from the Norwegian Population Statistics.

2.2. Statistical analyses

We estimated the risk of all-cause mortality and cancer related death among MS patients and controls using Cox proportional hazard regression. Hazard ratio (HR) with 95% confidence interval (CI) for the association between risks of all-cause mortality in general, and mortality following a primary cancer diagnosis specifically, were reported. The follow-up period were from the time the Cancer Registry of Norway was established in 1953 or subsequently from birth or immigration until date of death, emigration, or the end of follow-up on December 31, 2016.

To determine whether MS patients and controls express a difference between the means on continuous variables, we used Welch`s unequal variances t- test (Table 1), and chi square when measuring difference between MS patients and controls on categorical variables. For all-cause mortality following a primary cancer diagnosis, individuals surviving cancer were censored at date of emigration, death or end of follow-up, whichever occurred first. Sex, age, residence and attained educational level were the covariates used in both models: the all-cause mortality model and the mortality following a primary cancer diagnosis model. Model specific covariates for mortality following a primary cancer diagnosis were age at cancer diagnosis and year of cancer diagnosis. These time-dependent covariates were included to counteract immortal time bias towards MS patients who were collected in the sample at MS diagnosis, and hence were immortal until then. Time- dependent covariates in the analysis will adjust for possible time-dependent immortality in favour of MS patients.

The same covariates were used in an additional sub analysis model with cancer specific death as registered as underlying cause of death in the death certificate as the outcome (Table 2).

We generated categories of cancer based on data from the Cancer Registry of Norway originally based on ICD-7–10 into cancer in urinary organs (C64–C68), central nervous system cancer (CNS) (C70–C72); cancer in respiratory organs (C30-C39), breast cancer (C50), colorectal cancer (C18.0, C18.2–C18.9, C19.9, C20.9, C26.0), ovarian cancer (C56), haematological cancers including lymphoma, myeloma, hematopoietic or lymphatic cancer (C81–C96, D45–D46), “other” including skin (C43-44), female genital organs (C51-55, C57-58) excluding ovarian organs (C56) male genital organs (C60-63), digestive system (C15-C17, C21-C25) other than colorectal organs (C18.0, C18.2–C18.9, C19.9, C20.9, C26.0), bones and joints (C40-42, C45-C49), eye and adnexa (C69), thyroid and other endocrine glands (C73-C75), unspecified (C76-C80), oral cavity and larynx (C0-C14). Based on our previous studies on cancer risk in MS and controls (Grytten et al., 2020; Grytten et al., 2021), and reports of the frequency and severity of breast and colorectal cancers (Brenner et al., 2020), we considered these cancer subtypes of specific importance in the study of survival following a cancer diagnosis, and hence included these cancer types in our analyses.

The effect of education on risk of all-cause mortality in general and mortality following a cancer diagnosis is well established (Huisman et al., 2005) and was thus included in the multivariate model. We categorized level of education into primary level (10 years or less), secondary level (11–13 years), undergraduate level (14–17 years) and graduate level (18 years or more).

The statistical analyses were performed in IBM SPSS Statistics 26 (IBM Corp., Armonk, N.Y., USA).

3. Results

3.1. Cohort description

The sample comprised a total of 6950 MS patients of whom 778 (11.2%) had a cancer diagnosis, and 37,922 general population controls of whom 4017 (10.5%) had a cancer diagnosis (Table 1). Mean age at cancer diagnosis was 56.0 years (SD 11.9) for MS patients and 56.8 (SD 13.7) for the population controls (p=0.11). Most MS patients (57.1%) and controls (62.9%) were diagnosed with primary cancer during 2006 – 2016, and there was no difference in periods of cancer diagnosis between MS patients and controls (p=0.17). Mean age at death following a cancer diagnosis among MS patients was 63.9 years (SD 9.3) and 65.1 (SD 14.1) for the general population controls (p= 0.59). More MS patients (48.0%) than controls (41.9%) had attained secondary level education, and fewer MS patients (21.7%) than controls (26.7%) had attained undergraduate university/ college level (p< 0.001).

Table 1
Demographic and clinical data for all multiple sclerosis (MS) patients and population controls.

	Multiple sclerosis cohort		General population cohort	
	All (%)	Subjects with cancer	All (%)	Subjects with cancer
N (%)	6950	778 (11.3)	37922	4017 (10.6)
Dead 1953 – 2016 (%)	1468	322 (21.9)	1875	810 (43.2)
Female (%)	4638	537 (11.6)	25267	2617 (10.4)
Male (%)	2312	241 (10.4)	12665	1400 (11.1)
Mean age at cancer diagnosis (SD)		56.0 (11.9)		56.8 (13.7)
Age at cancer diagnosis category, n (%)				
19-49 years		204 (26.2)		1124 (28.0)
50-59 years		252 (32.4)		1037 (25.8)
60-69 years		229 (29.4)		1158 (28.8)
≥70 years		93 (12.0)		689 (17.4)
Cancer diagnosis period, n (%)				
1953 - 1985		29 (3.7)		189 (4.7)
1986 - 1995		80 (10.3)		340 (8.5)
1996 - 2005		225 (28.9)		961 (23.9)
2006 2016		444 (57.1)		2527 (62.9)
Mean time in years to death (SD)	55.61 (8.2)	57.9 (6.8)	56.8 (22.2)	60.5 (6.3)
Mean age at death (SD), 1953 – 2016	59.6 (11.5)	63.9 (9.3)	62.5 (SD 17.1)	65.1 (SD 14.0)
Average follow-up time from entry, years[2] (SD)	55.6 (8.2)	57.9 (6.8)	56.8 (22.2)	60.5 (6.3)
Educational level, n (%):	63 missing	3 missing		
Primary	1606 (23.2)	220 (28.3)	9185 (24.2)	1039 (25.9)
Secondary	3326 (48.0)	368 (47.3)	15892 (41.9)	1831 (45.6)
Undergraduate	1508 (21.7)	132 (17.0)	10138 (26.7)	897 (22.3)
Graduate	443 (6.4)	55 (7.1)	2707 (7.1)	250 (6.2)
Cancer: Malignant neoplasm of, n (%):				
Brain and central nervous system		49 (6.3)		190 (4.8)
Urinary organs		54 (7.0)		210 (5.2)
Respiratory organs		65 (8.3)		231 (5.8)
Hematological system		48 (6.1)		298 (7.4)
Ovarian organs		21 (2.6)		97 (2.4)
Female breast		160 (20.6)		837 (20.8)
Colorectal organs		71 (9.1)		450 (11.2)
Other*		311 (40.0)		1704 (42.4)

*Other included cancer diagnosis excluded from the analysis: skin, female genital organs other than ovarian organs, male genital organs, digestive system other than colorectal organs, bones and joints, mesothelium, eye and adnexa, endocrine glands, oral cavity and larynx, unspecified. SD= Standard Deviation.

3.2. All-cause mortality

The hazard ratio for all-cause mortality among MS patients compared to the matched general population controls was 4.97 (4.64 – 5.33); 5.08 (4.64 – 5.57) in women and 4.82 (4.34 – 5.35) in men (Table 2). Peak period for all-cause mortality in MS patients compared to controls was during 1975 – 1996, with HR: 5.06 (4.50 – 5.70), compared to the latest period from 1997 – 2016.

3.3. Mortality following a primary cancer diagnosis

The hazard ratio for mortality following a primary cancer diagnosis among MS patients compared to the matched general population controls was 2.61 (2.29 – 2.98): 2.73 (2.32 – 3.21) in women, and 2.41 (1.94 – 3.00) in men. A separate analyses of only cases with cancer as cause of death as declared on their death certificates, showed that the HR was 1.96 (1.67 – 2.98) (95% CI) among MS patients, compared to controls (Table 2).

The survival probability 10 years after cancer diagnosis was 60 % for MS patients and 82 % for controls. Twenty years after cancer diagnosis, the survival probability was 39% for MS patients and 75% for controls; 30 years after cancer diagnosis, 19% of MS patients and 52% of controls were still alive (Fig. 1).

Mortality following cancer diagnosis increased with age at diagnosis ≥ 70 years of age with HR: 1.51 (1.20 – 1.91) compared to the youngest category 19 – 49 year. Peak period for mortality in MS patients following a cancer diagnosis compared to controls was during 1963 - 1974, with HR: 2.05 (1.03 – 4.09), followed by a decline in mortality among those diagnosed with cancer during 1975 – 1996 with HR: 0.92 (0.69 – 1.23), compared to the latest period from 1997 – 2016.

Urinary cancer was associated with higher mortality in MS patients compared to controls, with HR: 2.53 (1.55 – 4.14). There was a non-significant increase in mortality among MS patients compared to controls, following cancer in the brain and nervous system, HR: 1.56 (0.86 – 2.85), in the respiratory organs, HR: 1.30 (0.93 – 1.85), and "other" **1.20 (0.96 – 1.47)**. Mortality was significantly increased among MS patients following haematological -, HR: 1.76 (1.08 – 2.88), female breast -, HR: 2.61 (1.85 – 3.68), ovarian -, HR: 2.30 (1.73-3.06) and colorectal – cancer, HR: 2.14 (1.47 – 3.11) (Table 2).

3.4. Attained educational level and mortality

All-cause mortality for both MS patients and controls was significantly associated with attained educational level (p for trend < 0.0001). The all-cause mortality gradually decreased with increasing attained educational level. HR (95% CI) for all-cause mortality was 2.85 (2.32 – 3.46) on primary educational level, HR: 1.71 (1.41 – 2.07) on secondary level and HR: 1.24 (1.00 – 2.07) on undergraduate level, compared to graduate level (Table 3).

Mortality following cancer diagnosis was significantly associated with attained educational level (p for trend <0.001). The HR for mortality following a cancer diagnosis among MS patients and controls with primary educational level was 2.14 (1.59 – 2.88), with secondary level HR was 1.38 (1.03 – 1.86) with undergraduate level HR was 1.30 (0.95 – 1.78) compared to those with attained graduate educational level (Table 3).

4. Discussion

In this long-term follow-up study, all-cause mortality was almost five-fold increased among MS patients, in both women and men with MS, and the mortality following a primary cancer diagnosis was more

Table 2
Adjusted hazard ratios (95% confidence intervals) for the association between multiple sclerosis (MS) and all-cause mortality (MS patients, n=6950, controls, n=37,922), and mortality following a primary cancer diagnosis (MS patients, n= 778, controls, n= 4017).

	MS versus matched controls
All-cause mortality[a]	4.97 (4.64 – 5.33)[e]
Male	4.82 (4.34 – 5.35)[e]
Female	5.08 (4.64 – 5.57)[e]
Period of death:	
1963 - 1974	NA
1975 - 1995	5.06 (4.50 – 5.70)[e]
1996 - 2016	Ref.
Mortality following a cancer diagnosis[b]**:**	
Cancer as cause of death certificate post mortem[c]	1.96 (1.67 – 2.98)[c]
Mortality following primary cancer diagnosis	2.61 (2.29 – 2.98)[c]
Male sex	2.41 (1.94 – 3.00)[c]
Female sex	2.73 (2.32 – 3.21)[c]
Age at cancer diagnosis[b]	
19-49 years	Ref
50-59 years	0.54 (0.53 – 0.76)[c]
60-69 years	0.74 (0.61 – 0.88)[c]
≥70 years	1.51 (1.20– 1.91)[c]
Age at death continuous	0.063 (0.054 – 0.075)[d]
Cancer diagnosis period[b]:	
1963 - 1974	2.05 (1.03 – 4.09)[f]
1975 - 1995	0.92 (0.69 – 1.23)
1996 – 2016	Ref.
Mortality following cancer diagnosis in:	
Brain and central nervous system	1.56 (0.86 – 2.85)
Urinary organs	2.53 (1.55 – 4.14)[e]
Respiratory organs	1.30 (0.93 – 1.85)
Hematological system	1.76 (1.08 – 2.88)[f]
Ovarian organs	2.30 (1.73 – 3.06)[d]
Breast	2.61 (1.85 – 3.68)[f]
Colorectal organs	2.14 (1.47 – 3.11)f
Other	**1.20 (0.96 – 1.47)**

[a] All-cause: total all-cause mortality adjusted for birth year, sex, residence. [b] Mortality following a primary cancer diagnosis adjusted for birth year, sex, residence, and the time-dependent covariate year of cancer diagnosis (continuous) and age at cancer diagnosis (continuous) to counteract immortal time bias, c: cancer as cause of death certificate
[d] : p<.000
[e] : p<.0.001
[f] : p = 0.03

than two-fold increased among MS patients, compared to the matched general population. There was a trend from 1995 towards end of follow-up of an improved survival from all-cause mortality, whilst mortality following a primary cancer diagnosis declined from 1975, among MS patients compared to controls. The possible decline in mortality among MS patients could be a result of improved health services in general, clinical awareness, earlier diagnosis and modern cancer and MS therapy.

Our finding of increased all-cause mortality among MS patients compared to the general population, is in concordance with previous studies (Burkill et al., 2017; Grytten, 2017; Grytten et al., 2019; Koch-Henriksen et al., 2017; Lunde et al., 2017). Also, our finding of increased mortality among MS patients following a cancer diagnosis is in concordance with other reports (Grytten Torkildsen et al., 2008; Lalmohamed et al., 2012; Lunde et al., 2017; Thormann et al., 2017). Previous studies have thus reported cancer related mortality in MS patients both as equal (Kingwell et al., 2020; Norgaard et al., 2019; Smestad et al., 2009) or lower than in controls (Bronnum-Hansen et al., 2004; Roshanisefat et al., 2015).

Previous inconsistency in reports of cancer related mortality among

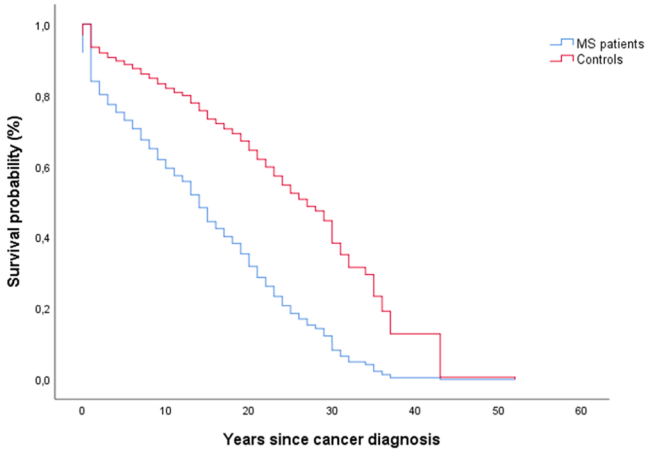

Fig. 1. Multivariate Cox regression on overall survival after a cancer diagnosis among multiple sclerosis patients and of controls, adjusted for sex, age, attained educational level, age of cancer diagnosis and year of cancer diagnosis. P <.001.

MS patients could, to some extent be explained by use of the use of heterogeneous outcome measures. Death certificates is widely used (Bronnum-Hansen et al., 2004; Grytten Torkildsen et al., 2008; Kingwell et al., 2020; Lunde et al., 2017; Smestad et al., 2009) with the possibility of underestimating cancer related mortality as reported in this paper. To counteract both the challenge of competing risk, and the possibility of underreporting of cancer-specific mortality in cause of death certificates, we used the model of all- cause mortality following a cancer diagnosis.

We observed increased mortality among MS patients following colorectal -, breast - ovarian and haematological cancer diagnosis in concordance to previous studies (Marrie et al., 2021a, b; Marrie et al., 2021c). However, our previous study reported decreased hazard of both bowel, breast and haematological cancer diagnosis (Grytten et al., 2019). This could possibly suggest delayed diagnosis (Marrie et al., 2009b) due to diagnostic neglect (Kingwell et al., 2012). Specifically, the increased mortality among MS patients following urinary – and colorectal cancer could be suggestive of diagnostic delay, as symptoms from these organs could easily be interpreted as MS symptoms both by patients and health care workers. However, a recent study from Ontario, Canada, found evidence for breast and colorectal cancers to be likely detected at early stage among MS patients (Groome et al., 2022). The issue of possible delay in cancer diagnosis among MS patients remains controversial.

Higher mortality among MS patients, both in general and related to cancer, could possibly be attributed to MS-patients reduced attained educational level compared to controls. Mortality was inversely associated with attained educational level, and is consistent with studies on educational inequalities and mortality (Huisman et al., 2005). To some extent, lower educational attainment could account for reduced survival among MS patients compared to controls. Educational level was inversely associated with mortality, also following a cancer diagnosis. The survival associated with higher education might be a result of favourable lifestyle habits, which influence an advantageous outcome. In addition, higher attained educational level has previously been associated with a lower risk of MS (Bjornevik et al., 2017). This also highlights the importance of including educational levels in mortality analyses.

The strengths of this study were the long follow-up period from 1953 to 2016, the registry- based methodology, and the population- based cohorts of MS and matched controls. In our study, we used two different measures of cancer related mortality, to avoid ascertainment bias (Table 2). In the sub-analysis we observed that cancer as cause of death registered in the death certificate obtained from the Cause of Death

Table 3
The Hazard Ratio (HR) and 95% Confidence intervals (CI) of all-cause mortality and mortality following a cancer diagnosis according to level of education among multiple sclerosis (MS) patients compared to matched population controls.

	MS patients vs. controls all- cause mortality		MS patients vs. controls mortality following cancer diagnosis	
	N. of events cases/ controls	HR (95% CI)[a]	N. events of cases/ controls	HR (95% CI)[a, b]
	1450/1875	Cases vs. controls	320/810	Cases vs. controls
Level of education:				
Primary	463/822	2.85 (2.32 – 3.46)	115/283	2.14 (1.59 – 2.88)
Secondary	708/757	1.71 (1.41 – 2.07)	146/344	1.38 (1.03 – 1.86)
Undergraduate	227/237	1.24 (1.00 – 2.07)	48/144	1.30 (0.95 – 1.78)
Graduate	52/59	Ref.	11/39	Ref.
P for trend		<0.000		<0.001

[a] Effect estimates calculated using Cox regression comparing level of education in patients and the matched controls to estimate the effect on cancer mortality.
[b] Adjusted for birth year, sex, residence, age at cancer diagnosis (continuous), cancer diagnosis period (continuous).

Registry was less reported, compared to all-cause mortality following a primary cancer diagnosis registered in the Norwegian Cancer Registry. The use of the Norwegian Cancer Registry from 1953, with mandatory data registration on all incidence cases from physicians nation-wide, the larger cohort and the long follow-up might explain our reports on higher hazards of mortality following cancer diagnosis.

Another challenge in comparing mortality following a cancer diagnosis among MS patients with the general population is that the general reduced life expectancy of MS patients (Lunde et al., 2017). We applied several strategies to overcome this challenge. First, this study provided a 65- year follow- up of cancer mortality. The long follow- up period allowed us to include full-length of the life spans of the oldest persons. Second, we used Cox proportional hazard regression to estimate the risk of mortality following a cancer diagnosis prospectively; where each of the cases were followed-up to censoring events as they occur subsequently. Third, we used the all-cause mortality approach rather than only cancer-related deaths on death certificates, to include all deaths, following the incident cancer cases obtained from the Norwegian Cancer registry (Roshanisefat et al., 2015).

A limitation to the analyses of all-cause mortality was the absence of age-dependent covariates, which would counteract immortal time bias and the overestimation of specifically all-cause mortality among MS patients. Contrary, in the analyses of mortality following a cancer diagnosis, potential immortal time bias was counteracted with the age-dependent covariates showing excess mortality following cancer diagnosis among MS patients aged 70 years or older. We did not have the opportunity to investigate a possible outcome of exposure to disease modulatory treatment (DMT), on the mortality among MS patients, which would be of consequential interest for cancer related mortality.

5. Conclusion

We found that although survival improved during recent years, all-cause mortality was five- fold, while mortality following a cancer diagnosis was two- fold among MS patients compared to controls. Lower education increased the risk of higher mortality among MS patients. Increased mortality in MS following female breast, ovarian, colorectal - and haematological cancer diagnosis could possibly be indicative of diagnostic neglect and consequently delayed diagnosis and treatment. Our results points out the need for raised diagnostic awareness of cancer risks, aiming at decreasing mortality among MS patients.

Ethical approval

The Western Norway Regional Committee for Medical and Health Research Ethics approved the study (REK Vest 2016/300).

Patients consent for publication

Not applicable.

Data availability statement

The database of the study is available for consultation or reuse on request to the principal investigator (N.G.). Sharing of all or part of this database is subject to prior authorization by the Western Norway Regional Ethics Committee.

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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. **Rune Midgard:** Data curation, Writing – review & editing. **Anita Vatne:** Data curation, Writing – review & editing. **Jan H. Aarseth:** Data curation, Writing – review & editing. **Janne Mannseth:** Writing – review & editing. **Øivind Torkildsen:** Conceptualization, Validation, Investigation, Writing – review & editing, Supervision, Funding acquisition.

Competing interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: N.G., T.R., J.H.A., A.V., R.M., and E.B. reports no disclosures. K. M.M. reports grants or personal fees from Biogen, Novartis, Roche, Teva and Sanofi, outside the submitted work. E.G.C. reports grants or personal fees from Almirall, Biogen, Merck, Novartis, Roche, Sanofi Genzyme and Teva, outside the submitted work. Ø.T. reports personal fees from Biogen, Merck, Sanofi, Roche, and Teva, outside the submitted work.

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