ORIGINAL ARTICLE

# All-cause mortality following a cancer diagnosis amongst multiple sclerosis patients: a Swedish population-based cohort study

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**Background and purpose:** A reduced cancer risk amongst patients with multiple sclerosis (MS) has been reported. Theoretically, this could represent a genuine reduction in risk or, alternatively, 'diagnostic neglect', where cancer is undiagnosed when symptoms are misattributed to MS.

**Objective:** Assess all-cause mortality risk following a cancer diagnosis in patients with MS compared with a cohort without MS.

**Patients:** A cohort of MS patients ($n$ = 19 364) and a cohort of the general population ($n$ = 192 519) were extracted from national Swedish registers from 1969 to 2005. All-cause mortality after cancer in MS was compared with the general population. Poisson regression analysis was conducted in the MS and non-MS cohorts separately. The models were adjusted for follow-up duration, year at entry, sex, region and socioeconomic index. The two cohorts were combined and differences in mortality risk were assessed using interaction testing.

**Results:** The adjusted relative risk (and 95% confidence interval) for all-cause mortality following a cancer diagnosis in MS patients (compared with MS patients without cancer) is 3.06 (2.86–3.27; $n$ = 1768) and amongst those without MS 5.73 (5.62–5.85; $n$ = 24 965). This lower magnitude mortality risk in the MS patients was confirmed by multiplicative interaction testing ($P < 0.001$).

**Conclusions:** A consistent pattern of lower magnitude of all-cause mortality risk following cancer in MS patients for a range of organ-specific cancer types was found. It suggests that cancer diagnoses tend not to be delayed in MS and diagnostic neglect is unlikely to account for the reduced cancer risk associated with MS. The lower magnitude cancer risk in MS may be due to disease-associated characteristics or exposures.

## Introduction

There appears to be a reduced cancer risk amongst patients with multiple sclerosis (MS) [1–3], but whether this is a genuine reduction in risk has not been completely resolved. One possibility is that symptoms of cancer are misinterpreted as those of MS, resulting in failure to identify the cancer and thus 'diagnostic neglect' [3]. This would lead to under-diagnosis of cancer or at least a delay in its diagnosis. Such a delay would be likely to result in higher cancer mortality consistent with diagnostic neglect [3]. An assessment of mortality following cancer will help to resolve the extent to which cancer diagnoses are delayed in MS patients and whether there is a genuine reduction in cancer risk.

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Previous studies of survival following cancer in MS patients have yielded inconsistent results, with risks for mortality that are increased [4,5] or decreased [6–8] or with no difference compared with the general population [9]. One difficulty in comparing mortality in MS patients with the general population is that MS in itself is associated with a notable reduction in life span by approximately 5–10 years [10]. This is one reason why use of cancer-specific mortality can be problematic, as MS-related mortality may represent a competing risk for cancer mortality. All-cause mortality has been described as an important marker of MS outcome and encompasses many aspects of disease progression [11]. Therefore, all-cause mortality following a cancer diagnosis was examined but using interaction testing to take into account average differences in life span amongst those with MS and a general population cohort. This is also important, as the association of cancer with all-cause mortality in MS patients is likely to be of lower magnitude than in the general population as other causes are more likely.

Another issue is that patients with MS have a different case mix for cancer compared with the general population, so examination of risk for organ-specific cancers as well as all cancers is important. An example of this is brain tumours, which unlike other cancer types appear to be overrepresented in MS patients [12]. In a previous study using the same material, it was found that brain tumours were diagnosed at an earlier age in MS patients and mortality was no worse than amongst the general population [12]. The conclusion was that this is because of more frequent imaging in MS patients resulting in a greater detection of tumours at an earlier stage, including those that are asymptomatic. Brain tumours are only included in overall risk estimation in this paper.

This study utilizes a cohort of Swedish MS patients and a matched general population cohort, where all-cause mortality risk following a primary cancer diagnosis is examined, taking overall mortality risk into account through interaction testing. In addition to addressing the issue of potential diagnostic neglect, this study provides more general information on cancer prognosis in MS patients.

## Patients and methods

### Data sources and identification of multiple sclerosis and general population cohorts

All subjects included in this study were drawn from national Swedish registers, which have been described previously [1,12,13]. Briefly, patients who received a diagnosis of MS in Sweden between 1969 and 2005 were identified through two complementary sources: the National Patient Register and the Swedish Multiple Sclerosis Register (SMSreg). The National Patient Register recorded hospital discharge diagnoses since 1964 with national coverage since 1987 [14]. The SMSreg contains clinical and demographic details for patients with MS, including information that can be used to confirm the accuracy of an MS diagnosis [1]. The SMSreg requires written informed consent for inclusion.

Patients with MS were individually matched with up to 12 individuals (a lower number was achieved in a minority of cases) from the general population without MS by date of birth, sex, region and vital status at the time of diagnosis.

### Identification of cancer diagnosis

Through the Swedish Cancer Register, details of cancer diagnoses were identified (see Appendix). This register was established in 1958 and records all newly diagnosed malignant tumours in Sweden. The completeness of the Swedish Cancer Register is high, and underreporting of cases is estimated to be <4% [15]. Different editions of the International Classification of Diseases (ICD) have been used in the registry but all are concerted to ICD-7 (Index 1). The region of residence was defined in terms of the catchment areas of the six regional cancer centres Stockholm, Malmö, Gothenburg, Linköping, Umea and Uppsala-Örebro [16].

### Vital status and socioeconomic index

The Total Population Register provided information on date of death and migration. A six-category socioeconomic index entry (manual workers, non-manual workers, professionals, self-employed, farmers and others) was based on occupation identified from the census nearest in time to study entry. All data were linked using the unique personal identity number issued to all Swedish residents [17].

### Study population

From amongst the original 20 543 with MS and 204 161 without, 1047 and 10 428 observations were excluded, respectively, due to a cancer diagnosis before the entry date. One member of the MS cohort and six members without MS were excluded due to inaccurate data. In total, 19 364 with MS and 192 519 without the diagnosis were included to the study. A total of 1768 MS patients and 24 965 from the general population cohort had a primary cancer diagnosis

after entry. Benign tumours were not considered in estimation of mortality risk after cancer (333 with MS and 3739 without MS). Cancer diagnoses recorded after death or based on autopsy findings were not included in the analysis, for 98 subjects from the MS cohort and 878 from the general population cohort. The number of person-years provided by subjects was 233 317 for the MS cohort and 2 664 450 for the general population cohort.

### Ethical permission

Karolinska Institutet regional ethics committee approved this study.

### Statistical analysis

Poisson regression was used to estimate relative risks and 95% confidence intervals for mortality after diagnosis of cancer. The relative risks were reported as unadjusted and as adjusted. The adjustment was for follow-up duration, year at entry, sex, regional cancer centre (six cancer centres) and socioeconomic index. The logarithm of accumulated person-years served as the offset variable. Attained age was the underlying time scale.

Follow-up time was started at study entry and was to the first cancer date, emigration, death or 31 December 2005, whichever occurred first. Follow-up time for subjects with a diagnosis of cancer was split as they were moved to the cohort with cancer risk from the date of their first cancer diagnosis and followed until date of second cancer, emigration, death or 31 December 2005, whichever occurred first. The association of cancer with all-cause mortality was first assessed in the MS and general population cohorts separately. Then the cohorts were combined for multiplicative interaction testing. The interaction of MS with cancer was adjusted for main effects (MS and cancer) as well as the other measures.

The analyses were for all cancer types combined and separately for more specific diagnoses (Index 1). Brain tumour diagnoses were only included in overall risk estimation, as a recent study using the same material to examine mortality risk for brain tumour was published in 2013 [12].

### Sensitivity analysis

To examine whether the results may be influenced by changes in treatment, including immunomodulatory therapy, the follow-up period was truncated to before 1996 and from this time onwards, as the first of the more recent therapies, interferon-β, was introduced in Sweden in 1996 [18].

An analysis was performed limiting subjects with MS to those included in the SMSreg, to ensure a high diagnostic accuracy for MS [1].

All tests were two-sided and $P < 0.05$ and 95% confidence intervals not including 1.00 were considered statistically significant. Statistical analysis was conducted using Stata/MP statistical software, version 11.2 (StataCorp, College Station, TX, USA).

## Results

### Subject characteristics

There were 211 883 subjects with full data for analysis (MS without cancer 19 364, MS with cancer 1768, general population without cancer 190 695 and general population with cancer 24 965). Some 9.1% of

**Table 1** Characteristics of the study subjects

| | Multiple sclerosis cohort | | General population cohort | |
|---|---|---|---|---|
| | All (%) | Subjects with cancer (%) | All (%) | Subjects with cancer (%) |
| *N* | 19 364 | 1768 | 192 519 | 24 965 |
| Female, % | 12 428 (63.7) | 1199 (67.82) | 123 256 (63.6) | 15 759 (12.79) |
| Age at MS diagnosis/entry | | | | |
| ≤20 | 3429 (17.7) | 155 (9.8) | 34 202 (17.1) | 1822 (7.3) |
| 21–30 | 4280 (22.1) | 268 (15.2) | 42 410 (22.1) | 3804 (15.2) |
| 31–40 | 4483 (23.2) | 418 (23.6) | 44 664 (23.2) | 6079 (24.4) |
| 41–50 | 3739 (19.3) | 468 (26.5) | 36 856 (19.1) | 6660 (26.7) |
| 51–60 | 2109 (10.9) | 302 (17.1) | 21 045 (10.9) | 4420 (17.7) |
| 61–70 | 1001 (5.2) | 132 (7.5) | 10 051 (5.2) | 1816 (7.3) |
| ≥71 | 323 (1.6) | 25 (1.3) | 3291 (1.7) | 464 (1.42) |
| Mean (SD) | 39.8 (±15.7) | 45.5 (±14.2) | 39.5 (±15.8) | 46.0 (±14.2) |
| Mean (SD) age at cancer diagnosis | | 60.5 (±13.4) | | 63.3 (±13.3) |
| Average follow-up time from entry, years*(SD) | 11.9 (±9.0) | 14.0 (±9.5) | 13.0 (±9.8) | 16.5 (±9.3) |

*Follow-up time was started at study entry and was to the first cancer date, emigration, death or 31 December 2005, whichever occurred first.

19 364 MS patients had a cancer diagnosis and the corresponding proportion in the general population cohort was 12.9% from amongst 192 519 (Table 1). Mean age and standard deviation (SD) at entry for 1768 MS patients with cancer (572 male and 958 female) was 45.5 (±14.2) years and mean disease duration was 14.0 (±9.5) years. Mean age at cancer diagnosis (SD) was 60.5 (±134) for MS and 63.3 (±13.3) in the general population.

### All-cause mortality after a primary cancer diagnosis in individuals with and without multiple sclerosis

All-cause mortality following a cancer diagnosis was estimated amongst those with and without MS separately. Table 2 shows that amongst those with MS the relative risk (and 95% confidence interval) for mortality following any cancer diagnosis is 3.06 (2.86–3.27) and the risk is notably higher in the non-MS cohort, at 5.73 (5.62–5.85). This lower relative risk of mortality following cancer amongst the MS cohort compared with the general population cohort was confirmed by multiplicative interaction testing (<0.001), when both cohorts were combined. A similar statistically significant lower relative risk of mortality following cancer in the MS cohort was observed for the cancers of specific organ systems, except for the kidney, urinary organs, endocrine, eye, nose or middle ear, but in some instances this may have been due to small numbers of subjects (Table 2).

Sensitivity analysis included division of the follow-up period by calendar year to before 1996 and from 1996, when immunomodulation therapy was recommended for MS treatment in Sweden. The risk estimates for the periods before 1996 (the number of events in subjects with MS was 1542) and from this time (the number of events in subjects with MS was 226) were broadly similar and statistically significant. The interaction analyses for these periods produced similar results of 0.50 (0.46–0.54), $P < 0.001$, for the earlier period and 0.49 (0.46–0.53), $P < 0.001$, for the later.

When subjects with MS were limited to those identified using the SMSreg the main findings were broadly similar (data not shown).

## Discussion

Although a diagnosis of cancer (all types combined) was associated with a raised relative risk of all-cause mortality in both the MS and general population cohorts (well known to be as high as 33%) [19], the magnitude of risk was lower amongst those with MS. A similar consistent pattern of lower magnitude risk of all-cause mortality amongst those with MS was found across a range of cancer types, with some exceptions. The results from multiplicative interaction testing provide more evidence that there is no greater mortality risk following cancer in MS patients compared with the general population. This suggests that in the majority of MS patients cancer diagnosis is not delayed, as this would tend to be associated with a worse prognosis and a higher mortality risk.

Previous findings have shown an inverse association between MS and cancer risk [1–3,20]. The reasons for this reduced risk are uncertain, but it has been suggested that cancer diagnoses may be missed or delayed in MS patients, resulting in a form of 'diagnostic neglect' [3]. Other studies have examined cancer-specific mortality in MS and also found lower risks for mortality than in the general population [21] or no difference with the general population [22]. However, a direct comparison of cause-specific mortality between those with and without MS can be problematic.

On average, the life span of patients with MS is shorter than that of the general population [23,24]. This excess mortality is due to several causes, including a 7.5 times higher risk of suicide [7,23,25]. The higher risk of mortality from other causes may result in a lower magnitude relative risk of mortality associated with cancer (all-cause or cancer specific), as observed. This bias was tackled in two ways. First, our outcome was all-cause mortality to avoid underestimation of cancer-specific mortality. Secondly, interaction analysis was performed to assess whether the difference in mortality risk following cancer was of lower magnitude amongst MS patients, even after taking into account differences in mortality risk compared with the general population. The results indicate that, even after taking these differences into account, there was no increased mortality risk following a cancer diagnosis compared with the general population. There is even evidence of the possibility that cancer survival may be better in patients with MS. This is consistent with the suggestion that cancer diagnoses are not more frequently delayed in this patient group.

The apparently lower magnitude of increased mortality risk following a cancer diagnosis in MS could indicate that the lower risk of cancer observed in MS is a genuine phenomenon rather than a diagnostic artefact. The reason for such a reduced cancer risk can only be speculation [1]. Tobacco is a well-known carcinogen associated with higher all-cause mortality risk in MS [26]. A lower mortality in MS after a lung cancer diagnosis was observed, although MS patients may have given up smoking at an earlier age as it is also linked with MS risk [27]. Higher body mass index (BMI) is a risk for some cancers [28], although the association of BMI with MS is inconsistent, with

**Table 2** Risk of all-cause mortality after diagnosis of cancer in the multiple sclerosis cohort compared with a general population cohort

| | MS cohort ($n$ = 19 364) | | | | General population cohort ($n$ = 192 519) | | | | Interaction | |
|---|---|---|---|---|---|---|---|---|---|---|
| Cancer site (ICD code) | Number of cancer (%)/ non-cancer (%) | Mortality events cancer (%)/ non-cancer (%) | Crude RR (95% CI) | Adjusted RR (95% CI)[a] | Number of cancer (%)/ non-cancer (%) | Mortality events cancer (%)/ non-cancer (%) | Crude RR (95% CI) | Adjusted RR (95% CI)[a] | Adjusted RR (95% CI) | $P$ value |
| Overall | 1768 (9.1)/ 17 596 (90.9) | 1134 (64.1)/ 6310 (32.6) | 3.91 (3.67–4.17) | 3.06 (2.86–3.27) | 24 965 (12.9)/ 167 554 (87.0) | 16 397 (65.7)/ 34 688 (18.2) | 7.96 (7.81–8.12) | 5.73 (5.62–5.85) | 0.51 (0.48–0.55) | <0.001 |
| Digestive cancer (150–159) | 280 (1.5)/ 19 084 (98.5) | 232 (82.9)/ 7212 (37.8) | 8.99 (7.83–10.18) | 4.42 (3.87–5.06) | 4820 (2.5)/ 187 699 (97.5) | 3959 (82.1)/ 47 126 (25.1) | 12.39 (11.99–12.80) | 6.66 (6.45–6.88) | 0.63 (0.55–0.73) | <0.001 |
| Respiratory cancer (160–164) | 95 (0.5)/ 19 027 (99.5) | 87 (91.6)/ 7357 (38.2) | 18.93 (15.32–23.39) | 14.17 (11.42–17.60) | 1858 (1.0)/ 190 661 (99.0) | 1747 (94.3)/ 49 338 (25.9) | 31.96 (30.47–33.53) | 25.75 (24.54–27.00) | 0.54 (0.43–0.68) | <0.001 |
| Breast cancer (170) | 314 (1.6)/ 19 050 (98.4) | 159 (50.6)/ 7285 (38.2) | 2.43 (2.01–2.83) | 2.00 (1.71–2.35) | 3724 (2.0)/ 188 795 (98.0) | 1956 (52.5)/ 49 129 (26.0) | 3.36 (3.21–3.52) | 3.10 (2.96–3.24) | 0.60 (0.52–0.73) | <0.001 |
| Female genital cancer (17, 172, 175) | 315 (1.6)/ 19 049 (98.4) | 144 (45.7)/ 7300 (38.3) | 0.80 (0.68–0.94) | 1.10 (0.93–1.30) | 3471 (1.8)/ 189 048 (98.2) | 1456 (41.9)/ 49 629 (26.2) | 1.12 (1.06–1.18) | 1.82 (1.72–1.92) | 0.54 (0.44–0.67) | <0.001 |
| Male genital cancer (177, 178) | 123 (0.6)/ 19 241 (99.4) | 85 (69.1)/ 7359 (35.3) | 1.26 (1.01–1.57) | 0.66 (0.53–0.80) | 2592 (1.4)/ 189 927 (98.6) | 1554 (59.9)/ 49 531 (26.0) | 1.52 (1.45–1.60) | 0.87 (0.83–0.92) | 0.74 (0.59–0.92) | <0.01 |
| Kidney cancer (180) | 32 (0.2)/ 19 332 (99.8) | 28 (87.5)/ 7416 (38.4) | 9.02 (6.22–13.07) | 4.22 (2.91–6.12) | 518 (0.3)/ 192 002 (99.7) | 427 (82.6)/ 50 658 (26.4) | 7.94 (7.22–8.74) | 5.18 (4.72–5.70) | 0.80 (0.54–1.16) | 0.210 |
| Urinary organ cancer excluding kidney (181) | 75 (0.4)/ 19 289 (99.6) | 53 (70.7)/ 7391 (38.3) | 4.11 (3.13–5.39) | 2.96 (2.25–3.88) | 847 (0.4)/ 191 672 (99.6) | 561 (66.3)/ 50 524 (26.4) | 4.61 (4.24–5.01) | 2.22 (2.04–2.42) | 1.28 (0.96–1.70) | 0.08 |
| Endocrine cancer (194, 195) | 36 (0.2)/ 19 328 (99.8) | 23 (63.9)/ 7421 (38.4) | 1.11 (0.78–1.60) | 1.34 (0.93–1.92) | 343 (0.2)/ 192 176 (99.8) | 151 (44.0)/ 50 934 (26.5) | 1.08 (0.94–1.22) | 1.13 (0.99–1.28) | 1.19 (0.82–1.74) | 0.35 |
| Bone and connective tissue cancer (196, 197) | 11 (0.05)/ 19 353 (99.05) | 8 (72.7)/ 7438 (38.4) | 1.70 (0.85–3.34) | 2.09 (1.04–4.18) | 184 (0.1)/ 192 335 (99.9) | 132 (71.7)/ 50 953 (26.5) | 2.20 (1.85–2.61) | 1.74 (1.46–2.061) | 1.23 (0.62–2.60) | 0.56 |
| Blood cancer (200–202, 203, 205) | 68 (0.3)/ 19 296 (99.7) | 50 (73.5)/ 7394 (38.3) | 1.77 (1.34–2.43) | 1.26 (0.95–1.66) | 1044 (0.5)/ 191 475 (99.5) | 807 (77.3)/ 50 278 (26.3) | 2.49 (2.33–2.67) | 2.12 (1.98–2.27)) | 0.58 (0.44–0.78) | <0.001 |
| Skin cancer (190, 191) | 165 (0.8)/ 19 199 (99.2) | 94 (57.0)/ 7350 (38.3) | 0.95 (1.14–1.29) | 0.61 (0.50–0.75) | 2417 (1.3)/ 190 102 (98.7) | 1167 (48.3)/ 49 918 (26.3) | 1.20 (1.14–1.28) | 0.71 (0.67–0.76) | 0.83 (0.68–1.01) | <0.001 |
| Eye, nose, middle ear cancer (160, 192) | 4 (0.02)/ 19 360 (99.98) | 1 (25.0)/ 7443 (38.4) | 0.57 (0.08–4.12) | 1.18 (0.16–8.40) | 75 (0.04)/ 192 444 (99.96) | 56 (74.0)/ 51 029 (26.0) | 2.27 (1.75–2.95) | 1.66 (1.29–2.16) | 0.60 (0.08–4.34) | 0.52 |

RR, relative risk; CI, confidence interval. [a]Adjusted for follow-up duration, year at entry, sex, regional cancer area (six cancer centres) and socioeconomic index.

higher BMI associated with an increased risk of onset [29] but lower BMI after onset [30–32]. There is no evidence that screening programmes, such as for breast or prostate cancer, involve greater participation by MS patients. The hypothesis that MS results in a greater risk of cancer symptoms being missed was tested. One interpretation of the findings is that the opposite occurs: the frequent medical contact to manage MS may result in earlier rather than later detection of cancer and thus an improved prognosis. This would also be consistent with a genuinely reduced cancer risk in MS [1]. It is speculated that cancer protection might partly result from the increase in systemic autoimmune responses such as against myelin antigens observed mong patients with MS [1].

The strengths of this study include its representativeness for MS patients in Sweden and the high level of precision offered by such large cohorts. The overall completeness of the cancer register in Sweden is also high [15], so it is unlikely that an important number of cancer diagnoses have been missed. Another advantage is that it was possible to compare mortality risk with a matched sample of the general population, using interaction testing to take into account differences in mortality not linked with cancer. It was also possible to adjust for measures associated with both cancer and mortality risk, including socioeconomic index. Possible regional differences in cancer diagnosis or survival were taken into account.

The study also has some potential limitations. It is possible that differences in cancer case mix between those with and without MS may influence the findings. Whilst this may be true for some specific cancer types [12], the results were consistent across a range of cancers, suggesting differences in case mix are unlikely to explain the main findings. Another possibility is that, rather than some cancer diagnoses being delayed, they are missed altogether more often amongst MS patients. Whilst this cannot be disproved, it seems unlikely that none of these cancer diagnoses would be made at a later time point as the disease progressed, but prior to death. It was not possible to examine influences of more recently introduced immunomodulatory therapy as these data were not available from the registers for the study period. However, the results were similar in periods before and after introduction of interferon-β1b in Sweden. It was not possible to identify the specific immunological characteristics or environmental exposures that may explain our findings.

## Conclusions

A lower magnitude risk of all-cause mortality following a cancer diagnosis in MS compared with mortality risk following a cancer diagnosis in a general population sample was found, suggesting that cancer diagnoses tend not to be more delayed in MS patients. This in turn suggests that cancer is not consistently missed in this patient group and that the lower cancer risk reported in MS is not the result of 'diagnostic neglect', thus providing more evidence of a genuinely reduced cancer risk in MS.

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## Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

## References

1. Bahmanyar S, Montgomery SM, Hillert J, Ekbom A, Olsson T. Cancer risk among patients with multiple sclerosis and their parents. *Neurology* 2009; **72:** 1170–1177.
2. Nielsen NM, Rostgaard K, Rasmussen S, *et al*. Cancer risk among patients with multiple sclerosis: a population-based register study. *Int J Cancer* 2006; **118:** 979–984.
3. Kingwell E, Bajdik C, Phillips N, *et al*. Cancer risk in multiple sclerosis: findings from British Columbia, Canada. *Brain* 2012; **135**(Pt 10)**:** 2973–2979.
4. Lalmohamed A, Bazelier MT, Van Staa TP, *et al*. Causes of death in patients with multiple sclerosis and matched referent subjects: a population-based cohort study. *Eur J Neurol* 2012; **19:** 1007–1014.
5. Grytten Torkildsen N, Lie SA, Aarseth JH, Nyland H, Myhr KM. Survival and cause of death in multiple sclerosis: results from a 50-year follow-up in Western Norway. *Mult Scler* 2008; **14:** 1191–1198.
6. Palo J, Duchesne J, Wikström J. Malignant diseases among patients with multiple sclerosis. *J Neurol* 1977; **216:** 217–222.
7. Brønnum-Hansen H, Koch-Henriksen N, Stenager E. Trends in survival and cause of death in Danish patients with multiple sclerosis. *Brain* 2004; **127:** 844–850.
8. Westlund K. Distribution and mortality time trend of multiple sclerosis and some other diseases in Norway. *Acta Neurol Scand* 1970; **46:** 455–483.
9. Smestad C, Sandvik L, Celius EG. Excess mortality and cause of death in a cohort of Norwegian multiple sclerosis patients. *Mult Scler* 2009; **15:** 1263–1270.
10. Bronnum-Hansen H, Koch-Henriksen N, Stenager E. Trends in survival and cause of death in Danish patients with multiple sclerosis. *Brain* 2004; **4**(Pt 4)**:** 844–850.
11. Scalfari A, Knappertz V, Cutter G, Goodin DS, Ashton R, Ebers GC. Mortality in patients with multiple sclerosis. *Neurology* 2013; **81:** 184–192.
12. Montgomery S, Hassan A, Bahmanyar S, *et al*. Mortality following a brain tumour diagnosis in patients with multiple sclerosis. *BMJ open* 2013; **3:** e003622.
13. Montgomery S, Hillert J, Bahmanyar S. Hospital admission due to infections in multiple sclerosis patients. *Eur J Neurol* 2013; **20:** 1153–1160.

14. Ludvigsson JF, Andersson E, Ekbom A, *et al*. External review and validation of the Swedish national inpatient register. *BMC public health* 2011; **11:** 450.
15. Barlow L, Westergren K, Holmberg L, Talback M. The completeness of the Swedish Cancer Register: a sample survey for year 1998. *Acta oncol* 2009; **48:** 27–33.
16. The National Board of Health and Welfare. Cancer Register in Sweden. Publikationer 2011/Cancer i Sverige 2014. http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/18274/2011-3-26.pdf (accessed 01/05/2014).
17. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol* 2009; **24:** 659–667.
18. Andersen O. From the Gothenburg cohort to the Swedish multiple sclerosis registry. *Acta Neurol Scand Suppl* 2012; **195:** 13–19.
19. Hardee JP, Porter RR, Sui X, *et al*. The effect of resistance exercise on all-cause mortality in cancer survivors. *Mayo Clin Proc* 2014; **89:** 1108–1115.
20. Lebrun C, Vermersch P, Brassat D, *et al*. Cancer and multiple sclerosis in the era of disease-modifying treatments. *J Neurol* 2011; **258:** 1304–1311.
21. Koch-Henriksen N, Bronnum-Hansen H, Stenager E. Underlying cause of death in Danish patients with multiple sclerosis: results from the Danish Multiple Sclerosis Registry. *J Neurol Neurosurg Psychiatry* 1998; **65:** 56–59.
22. Sun LM, Lin CL, Chung CJ, Liang JA, Sung FC, Kao CH. Increased breast cancer risk for patients with multiple sclerosis: a nationwide population-based cohort study. *Eur J Neurol* 2014; **21:** 238–244.
23. Rodriguez-Antiguedad Zarranz A, Mendibe Bilbao M, Llarena Gonzalez C, Audicana C. Mortality and cause of death in multiple sclerosis: findings from a prospective population-based cohort in Bizkaia, Basque Country, Spain. *Neuroepidemiology* 2014; **42:** 219–225.
24. Scalfari A, Neuhaus A, Degenhardt A, *et al*. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. *Brain* 2010; **7** (Pt 7)**:** 1914–1929.
25. Jick SS, Li L, Falcone GJ, Vassilev ZP, Wallander MA. Mortality of patients with multiple sclerosis: a cohort study in UK primary care. *J Neurol* 2014; **261:** 1508–1517.
26. Manouchehrinia A, Weston M, Tench CR, Britton J, Constantinescu CS. Tobacco smoking and excess mortality in multiple sclerosis: a cohort study. *J Neurol Neurosurg Psychiatry* 2014; **85:** 1091–1095.
27. Hedstrom AK, Hillert J, Olsson T, Alfredsson L. Smoking and multiple sclerosis susceptibility. *Eur J Epidemiol* 2013; **28:** 867–874.
28. Ceschi M, Gutzwiller F, Moch H, Eichholzer M, Probst-Hensch NM. Epidemiology and pathophysiology of obesity as cause of cancer. *Swiss Med Wkly* 2007; **137:** 50–56.
29. Hedström AK, Olsson T, Alfredsson L. High body mass index before age 20 is associated with increased risk for multiple sclerosis in both men and women. *Mult Scler* 2012; **18:** 1334–1336.
30. Ghadirian P, Jain M, Ducic S, Shatenstein B, Morisset R. Nutritional factors in the aetiology of multiple sclerosis: a case–control study in Montreal, Canada. *Int J Epidemiol* 1998; **27:** 845–852.
31. Formica C, Cosman F, Nieves J, Herbert J, Lindsay R. Reduced bone mass and fat-free mass in women with multiple sclerosis: effects of ambulatory status and glucocorticoid use. *Calcif Tissue Int* 1997; **61:** 129–133.
32. Nortvedt MW, Riise T, Maeland JG. Multiple sclerosis and lifestyle factors: the Hordaland Health Study. *Neurol Sci* 2005; **26:** 334–339.1

## Appendix

### The following ICD codes have been used to identify cancer diagnosis used in the analysis.

| Type of cancer | ICD-7 |
|---|---|
| Digestive cancer | (150–159) |
| Respiratory cancer | (160–164) |
| Breast cancer | (170) |
| Female genital cancer | (17, 172, 175) |
| Male genital cancer | (177, 178) |
| Kidney cancer | (180) |
| Urinary organ cancer excluding kidney | (181) |
| Endocrine cancer | (194, 195) |
| Bone and connective tissue cancer | (196, 197) |
| Blood cancer | (200–202, 203, 205) |
| Skin cancer | (190, 191) |
| Eye, nose, middle ear cancer | (160, 192) |