Int. J. Cancer: **118,** 979–984 (2006)
© 2005 Wiley-Liss, Inc.

Cancer risk among patients with multiple sclerosis: A population-based register study

Nete Munk Nielsen[1]*, Klaus Rostgaard[1], Søren Rasmussen[2,3], Nils Koch-Henriksen[3,4], Hans H. Storm[5], Mads Melbye[1] and Henrik Hjalgrim[1]

[1]*Department of Epidemiology Research, Statens Serum Institut, Copenhagen, Denmark*
[2]*National Institute of Public Health, Copenhagen, Denmark*
[3]*The Danish Multiple Sclerosis Registry, Copenhagen, Denmark*
[4]*Department of Neurology, Aarhus University Hospital in Aalborg, Aalborg, Denmark*
[5]*Cancer Prevention and Documentation, Danish Cancer Society, Copenhagen, Denmark*

Cancer occurrence in patients with multiple sclerosis (MS) has been little studied, but associations with brain tumours, breast cancer, Hodgkin lymphoma and nasopharyngeal carcinoma have been suggested. We took advantage of population-based registers of MS and cancer to assess the risk of cancer following diagnosis of MS. Patients registered in the Danish Multiple Sclerosis Register were linked with the Danish Cancer Register to obtain information on cancer occurrence. The ratio of the observed to the number of expected cancers based on population-based incidence rates, *i.e.*, the standardised incidence ratio (SIR), served as measure of the relative cancer risk. A database comprising all Danish women born after April 1, 1935, with information on all live-born children, was used in the analyses of breast cancer to adjust for reproductive factors. Overall 1,037 cancers were observed in 11,817 MS patients during 153,875 person-years of follow-up *vs.* an expected number of 1,098 (SIR = 0.94 [95% confidence interval CI: (0.89–1.00)]. The risk of brain tumours and Hodgkin lymphoma was not increased. A 16% overall reduced cancer risk in men with MS was explained by reduced numbers of cancers of the digestive, respiratory and genital organs. Though the overall cancer risk was not increased [SIR = 1.01(0.94–1.09), *n* = 676], female MS patients had an increased risk of breast cancer [SIR = 1.21 (1.05–1.39), *n* = 193]. Adjusting for parity and age at first child delivery did not change this risk estimate materially. In general MS patients are not at increased risk of cancer. Women with MS, however, seem to have a small excess risk of breast cancer, which cannot be attributed to reduced parity or delayed first child birth.
© *2005 Wiley-Liss, Inc.*

Key words: MS; cancer; breast cancer; parity

Multiple sclerosis (MS) is a chronic demyelinating disease, characterised by relapsing neurological symptoms from different parts of the central nervous system (CNS). MS often presents in early adulthood, and despite episodes of remittance, the disease typically progresses and results in severe disability.[1]

Worldwide the geographical distribution of MS is uneven. Northern and central Europe, the northern US, Canada and south eastern Australia are considered high-risk regions, whereas Africa, Asia, Alaska and northern South America are low-risk regions.[2,3] Recent studies have indicated that MS incidence is increasing in several regions of the world.[3–10] Together with increased longevity of MS patients,[11] this will lead to a higher prevalence of MS worldwide, emphasizing the need for updated knowledge about comorbidity in this population.

Little is known about the overall cancer incidence among MS patients as most of previous studies have focused on the possible co-occurrence of MS and Hodgkin lymphoma.[12–14] Overall, MS patients do not seem to be at an increased risk of developing neither cancer in general, nor Hodgkin lymphoma in particular,[15–17] but increased risks of breast cancer,[15,16] cancers of the CNS,[16,18] the urinary tract system[16] and nasopharynx[16] have been suggested. Typically such observations have been based on a small number of cases, rendering the risk estimates statistically imprecise. Moreover, in breast cancer analyses important confounders such as parity have not been taken into consideration.[15,16]

We took advantage of 2 population-based disease registers, the Danish Cancer Register and the Danish Multiple Sclerosis Register, to assess the occurrence of cancer among Danish MS patients. Adjustment for parity was carried out using a population-based parity database on all Danish women born since 1935.

Material and methods

Since April 1, 1968, all Danish citizens have been given a unique identification number (CRS number), which is recorded together with continuously updated information on, *e.g.*, vital status, place of birth and place of residence in the Danish Civil Registration System (CRS).[19] The CRS numbers were used to identify persons in all the registries mentioned below and provided a means for register linkages.

Registers

The Danish Multiple Sclerosis Registry (DMSR) was formally established in 1956 but started operating in 1949 with a nationwide survey of prevalent cases of MS.[20] DMSR is based on notification from all hospital departments of neurology in Denmark, including MS rehabilitation centres, departments of pathology and practising neurologists. Since the establishment in 1977 of the National Hospital Discharge Register, the data collection has been supplemented annually with information on patients with MS admitted to Danish hospitals. Diagnoses of patients with disease onset before 1994 have been evaluated using the diagnostic criteria of Allison and Millar,[21,22] whereas cases with onset after 1993 have been evaluated employing the Poser criteria.[23] Only cases fulfilling the diagnostic criteria of Allison and Millar or Poser (including possible MS) are considered MS cases.[6,20] The change of diagnostic criteria in 1994 has not affected the consistency of the diagnosis over time. Thus, the percentage of cases reported to DMSR who did not comply with the contemporary diagnostic criteria was 23.3 before 1994 and 22.7 thereafter. Furthermore 2 neurologists have classified all reported cases with onset after 1965 (personal communication, Nils Koch-Henriksen). The DMSR is the longest running population-based MS register in the world and is estimated to be more than 90% complete with a diagnostic validity of 94%.[20]

The Danish Cancer Register is a population-based register containing data on incident cases of cancer throughout Denmark since 1943.[24] Details of individual cases of cancer are available accord-

Grant sponsor: Fonden til Lægevidenskabens Fremme; Grant number: 01074.
***Correspondence to:** Department of Epidemiology Research, Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark
Fax: +4532683165. E-mail: NMN@ssi.dk
Received 20 October 2004; Accepted after revision 6 June 2005
DOI 10.1002/ijc.21437
Published online 8 September 2005 in Wiley InterScience (www.interscience.wiley.com).

ing to the 7th revision of the international classification of diseases (ICD) for all years, and in addition according to the ICD-O since 1978.

The DMRS was linked with the Danish Cancer Register to identify all cases of cancer occurring in patients registered with MS. In the statistical analyses, the MS patients were followed for cancer occurrence from April 1, 1968, or MS diagnosis, whichever came later, until the date of death, emigration or December 31, 1997, whichever came first. The ratio of the number of observed to the number of expected cancers, *i.e*., the standardised incidence ratio (SIR), served as measure of the relative risk of cancer in the cohort. The expected number of cancers in the cohort was calculated as the sum of the sex-, age- and period-specific person-years at risk in the cohort multiplied by correspondingly stratified national cancer incidence rates. Ninety-five percent confidence intervals (95% CIs) for the SIRs were estimated by means of Wald's test assuming a Poisson distribution of the observed cases.

A more detailed analysis including adjustment for parity was carried out for breast cancer using a research database comprising all Danish women born between April 1, 1935, and March 31, 1978.[25] For every woman in this database, details on live-born children, *e.g*., birth dates are registered. Follow-up for breast cancer started on April 1, 1968, or on the person's 12th birthday, whichever came later, and continued until breast cancer diagnosis, death, emigration or December 31, 1995. MS cases among women in the research database were identified by linkage with the DMSR. The possible effect of MS on breast cancer risk was investigated using log-linear Poisson regression. Ratios of the incidence of breast cancer in women with MS to that in women without MS served as measure of the relative risk (RR). Analyses were carried out using the proc GENMOD procedure in SAS, and adjustment was made for age (12–14,15–19,20–24 , ... , 55+), calendar period (1968–1972, 1973–1977 , ... , 1993–1995), parity (0, 1, 2, 3, 4+) and age at delivery of the first child (12 to 19, 20 to 24, 25 to 29, 30 to 34, 35+; years).

Finally, analyses stratified by stage at diagnosis were also performed for breast cancer. Information on tumour size was obtained from the Danish Breast Cancer Cooperative Group (DBCG).[26] This register includes information of the histopathology, tumour size and lymph node involvement in the majority (82%) of breast cancer cases diagnosed in Denmark since 1978.[27]

Results

MS patients (11,817; 4,629 men and 7,188 women) that were alive on April 1, 1968, or later were followed for cancer occurrence for an average of 13 years, yielding a total of 153,875 person- years at risk. Overall 1,037 cases of cancer were observed among the MS patients, corresponding well with the 1,098 cancers expected [SIR = 0.94 (0.89–1.00)] (Table I). Cancer subtype-specific analyses revealed an increased risk of breast cancer [SIR = 1.21 (1.06–1.40), $n = 195$] and a decreased risk of cancers of the respiratory system [SIR = 0.63 (0.51–0.77), $n = 95$], digestive organs [SIR = 0.80 (0.70–0.93), $n = 180$] and of the male genital organs [SIR = 0.54 (0.36–0.80), $n = 24$] (Table I). No statistically significantly deviating risks were seen for cancers of the central nervous system [SIR = 1.00 (0.70–1.43), $n = 30$] or of the nasopharynx [SIR = 1.97 (0.49–7.88), $n = 2$] (Table I). As reported previously, we found no increased risk of haematopoietic and lymphatic cancers in the cohort.[17]

Men with MS were at statistically significantly reduced risk of cancer overall (SIR = 0.84 (0.76–0.93), $n = 361$], reflecting low risk of cancers of the digestive and respiratory systems and the genital organs (Table I).

No unusual overall cancer risk was observed in women with MS. However, increased risks of breast cancer [SIR = 1.21 (1.05–1.39), $n = 193$] and of nasopharyngeal cancer [SIR = 5.02 (1.26–20.09), $n = 2$] were noted. Neither age nor time since MS diagnosis influenced the breast cancer risk estimates (data not shown). Interestingly, women with MS had a 34% reduced risk of ovarian cancers [SIR = 0.66 (0.44–1.00), $n = 23$] (Table I).

Overall the risk of bladder cancer was not statistically significantly increased [SIR = 1.19 (0.93–1.51], $n = 66$). Because of earlier reports of an association between MS and bladder cancer, we examined the significance of age at and time since MS diagnosis. No clear patterns in the variation were observed. Thus, being diagnosed with MS from the age of 30 to 39 years was associated with an increased risk of bladder cancer in women [SIR = 2.69 (1.53–4.73), $n = 12$] but not in men. Likewise female MS patients had an increased risk of bladder cancer more than 10 years after MS onset [SIR = 1.58 (1.04–2.40), $n = 22$], whereas in men the risk of bladder cancer was increased 1 to 9 years after MS diagnosis [SIR = 2.09 (1.23–3.52), $n = 14$] (Table II).

Breast cancer-specific analyses

Information on reproductive history was available for all Danish women born since April 1, 1935 ($n = 1{,}517{,}655$). Of the total of 7,188 female MS-patients, who were followed in the present study, 3,318 were born since April 1, 1935. The analyses showed a 1.6-fold increased risk of breast cancer in women with MS [RR = 1.56 (1.19–2.06), $n = 51$)] (Table III). Adjustment for parity and age at delivery of first child did not change this estimate [RR = 1.54 (1.17–2.03)] (Table III).

Analyses including information on tumour size at time of diagnosis (available for 38,798 women diagnosed with breast cancer from 1978 to 1997 between the ages 35 and 70 years, including 102 women with MS) showed MS patients to have larger tumours at diagnosis than other women. Accordingly 27%, 57% and 16% of the women with MS were diagnosed with tumours measuring <1, 2–4 and 5+ cm, respectively, as compared to 39%, 50% and 11%, respectively, in women without MS (Cochran-Mantel-Haenszel test $p < 0.05$, adjusted for age; 35–49 years, 50–70 years).

Discussion

Overall, we found no evidence of an increased risk of cancer after a diagnosis of MS. In fact, men with MS had a slightly but statistically significantly reduced risk of cancer, whereas no unusual cancer risk was seen in women with MS.

Previous studies have focused on the possible associations between MS and CNS tumours,[16,18] bladder cancers,[16] cancers of the haematopoitic and lymphatic system,[12–14] breast cancers[15,16] and nasopharyngeal cancers.[16] In our study, the observed number of CNS tumours, bladder cancers and haematopoietic-lymphatic malignancies did not exceed the expected. We did., however, observed an increased risk of breast cancer in female MS patients and interestingly a reduced risk of cancers of the digestive, respiratory and genital organs among male MS patients.

We cannot rule out that our findings could be due to chance. However, we speculate that they may result from special circumstances and changed living conditions following MS such as medication, hormones and lifestyle-related risk phenomena including smoking, nutritional habits, reproductive factors and socioeconomic status.

MS patients are exposed to many different kinds and combinations of drugs. Several epidemiologic studies have suggested that long-term users of NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) have a lower risk of colorectal cancers compared to nonusers.[28–30] Although observations are less compelling NSAIDs may also have a protective effect against certain non-gastrointestinal cancer such as cancers of the lung,[31] prostate,[32] breast[31,33,34] and ovary.[29,35] The suggested inverse association between NSAIDs usage and cancer risk is compatible with the reduced risk of cancers of the digestive, respiratory and genital organs observed in the present investigation but not with the increased risk of breast cancer. Other kinds of medications such as hormone therapy

TABLE I – OBSERVED AND EXPECTED NUMBER OF CANCERS AND STANDARDISED INCIDENCE RATIOS IN A COHORT OF MS PATIENTS, BY SEX AND ANATOMICAL SITES

	Men and women			Men			Women		
	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)	Obs	Exp	SIR (95% CI)
All cancers	1037	1098.2	0.94 (0.89–1.00)	361	430.95	0.84 (0.76–0.93)	676	667.22	1.01 (0.94–1.09)
Buccal cavity	20	21.35	0.94 (0.60–1.45)	13	13.60	0.96 (0.56–1.65)	7	7.76	0.90 (0.43–1.89)
Nasopharynx	2	1.01	1.97 (0.49–7.88)	0	0.62	—	2	0.40	5.02 (1.26–20.09)
Digestive organs	180	223.66	0.80 (0.70–0.93)	75	100.68	0.74 (0.59–0.93)	105	122.98	0.85 (0.71–1.03)
Respiratory organs	95	151.64	0.63 (0.51–0.77)	51	94.27	0.54 (0.41–0.71)	44	57.38	0.77 (0.57–1.03)
Breast	195	160.51	1.21 (1.06–1.40)	2	0.68	2.95 (0.74–11.8)	193	159.83	1.21 (1.05–1.39)
Male genital organs	24	44.86	0.54 (0.36–0.80)	24	44.86	0.54 (0.36–0.80)	—	—	—
Prostate	20	37.67	0.53 (0.34–0.82)	20	37.67	0.53 (0.34–0.82)	—	—	—
Testis	4	5.77	0.69 (0.26–1.85)	4	5.77	0.69 (0.26–1.85)	—	—	—
Female genital organs	100	115.32	0.87 (0.71–1.05)	—	—	—	100	115.32	0.87 (0.71–1.05)
Cervix Uteri	40	36.05	1.11 (0.81–1.51)	—	—	—	40	36.05	1.11 (0.81–1.51)
Corpus Uteri	33	37.74	0.87 (0.62–1.23)	—	—	—	33	37.74	0.87 (0.62–1.23)
Ovary	23	34.66	0.66 (0.44–1.00)	—	—	—	23	34.66	0.66 (0.44–1.00)
Urinary organs	96	83.86	1.14 (0.94–1.40)	56	52.21	1.07 (0.83–1.39)	40	31.65	1.26 (0.93–1.72)
Kidney	30	28.39	1.06 (0.74–1.51)	14	14.02	1.00 (0.59–1.69)	16	14.37	1.11 (0.68–1.82)
Bladder	66	55.47	1.19 (0.93–1.51)	42	38.19	1.10 (0.81–1.49)	24	17.28	1.39 (0.93–2.07)
Skin	190	168.64	1.13 (0.98–1.30)	80	70.07	1.14 (0.92–1.42)	110	98.57	1.12 (0.93–1.35)
Melanoma	29	27.59	1.05 (0.73–1.51)	10	9.16	1.09 (0.59–2.03)	19	18.43	1.03 (0.66–1.62)
Other skin cancers	161	141.05	1.14 (0.98–1.33)	70	60.90	1.15 (0.91–1.45)	91	80.15	1.14 (0.92–1.39)
Eye	5	2.66	1.88 (0.78–4.51)	3	1.14	2.64 (0.85–8.19)	2	1.53	1.31 (0.33–5.24)
Brain and nervous system	30	29.97	1.00 (0.70–1.43)	8	11.71	0.68 (0.34–1.37)	22	18.26	1.20 (0.79–1.83)
Lymphatic and haem. tissue	61	58.44	1.04 (0.81–1.34)	28	27.51	1.02 (0.70–1.47)	33	30.93	1.07 (0.76–1.50)
Non-Hodgkins lymphoma	20	21.63	0.92 (0.60–1.43)	7	9.42	0.74 (0.35–1.56)	13	12.20	1.07 (0.62–1.83)
Hodgkin's disease	6	4.29	1.40 (0.63–3.12)	3	2.33	1.29 (0.41–3.99)	3	1.95	1.54 (0.50–4.76)
Leukaemia	27	21.63	1.25 (0.86–1.82)	15	10.74	1.40 (0.84–2.32)	12	10.90	1.10 (0.63–1.94)
Others[1]	41	37.29	1.10 (0.81–1.49)	21	14.22	1.48 (0.96–2.25)	20	23.01	0.87 (0.56–1.35)

[1]Endocrine glands, bone, connective tissue, secondary and unspecified sites.

TABLE II – OBSERVED AND EXPECTED NUMBER OF BLADDER CANCER IN A COHORT OF MS PATIENTS ACCORDING TO SEX, AGE AT MS DIAGNOSIS, TIME SINCE MS DIAGNOSIS AND PERIOD OF BLADDER CANCER DIAGNOSIS

	Male				Female			
	Obs	Exp	SIR (95% CI)		Obs	Exp	SIR (95% CI)	
Age at MS diagnosis								
<30 years	4	4.54	0.88 (0.33–2.35)	$p = 0.9$	4	2.42	1.65 (0.62–4.40)	$p < 0.05$
30–39 years	13	10.39	1.25 (0.73–2.15)		12	4.47	2.69 (1.53–4.73)	
40–49 years	15	13.35	1.12 (0.68–1.86)		5	5.90	0.85 (0.35–2.04)	
50+ years	10	9.91	1.01 (0.54–1.88)		3	4.49	0.67 (0.22–2.07)	
Time since MS diagnosis								
0–11 months	0	0.56	—	$p = 0.07$	0	0.27	—	$p = 0.2$
1–4 years	6	2.65	2.26 (1.02–5.03)		0	1.25	—	
5–9 years	8	4.06	1.97 (0.99–3.94)		2	1.83	1.10 (0.27–4.38)	
10+ years	28	30.91	0.91 (0.63–1.31)		22	13.93	1.58 (1.04–2.40)	
Period of cancer diagnosis								
1968–1977	13	8.18	1.59 (0.92–2.74)	$p < 0.05$	4	3.22	1.24 (0.47–3.31)	$p = 0.97$
1978–1987	19	12.97	1.46 (0.93–2.30)		8	5.59	1.43 (0.72–2.86)	
1988–1997	10	17.20	0.58 (0.31–1.08)		12	8.52	1.41 (0.80–2.48)	

TABLE III – ADJUSTED RELATIVE RISK (RR) OF BREAST CANCER IN WOMEN WITH A HISTORY OF MS (n = 3,318) AND INFORMATION ABOUT PARITY

	Number of cancers	RR (95% CI)[1]	Test for homogeneity	RR (95% CI)[2]	Test for homogeneity
Total					
History of MS	51	1.56 (1.19–2.06)	$p = 0.003$	1.54 (1.17–2.03)	$p = 0.004$
No MS	14,682	1		1	
Age at MS diagnosis					
<30 years	17	2.07 (1.29–3.33)	$p = 0.03$	1.99 (1.24–3.21)	$p = 0.04$
30–39 years	17	1.35 (0.84–2.18)		1.35 (0.84–2.17)	
40–49 years	14	1.40 (0.83–2.36)		1.38 (0.81–2.32)	
50+ years	3	1.65 (0.53–5.12)		1.64 (0.53–5.10)	
No MS		1.00		1.00	
Time since MS diagnosis					
0–11 months	5	2.34 (0.97–5.62)	$p = 0.04$	2.32 (0.97–5.57)	$p = 0.05$
1–4 years	12	1.52 (0.86–2.67)		1.51 (0.85–2.65)	
5–9 years	10	1.23 (0.66–2.28)		1.22 (0.65–2.26)	
10+ years	24	1.67 (1.12–2.49)		1.62 (1.09–2.42)	
No MS		1.00		1.00	

[1]Adjusted for woman's age, and calendar period.–[2]Adjusted for parity, age at first birth, woman's age, and calendar period.

might, however, contribute to the latter observation.[36–40] Also, long-term usage of oral contraceptives would be compatible with the observed reduced risk of ovarian cancer.[41]

MS patients in Denmark are recommended a diet rich in fruit and vegetables, and sparse in animal fat,[42] factors which might have a preventive effect on several cancer types.[43] In addition, smoking has been suggested to aggravate MS symptoms.[44] Thus, a decreased risk of cancers of the respiratory system could be associated with smoking abstinence and a cancer protective diet among MS patients.

Reproductive factors are known to be associated with the risk of breast cancer.[45] A chronic condition such as MS could affect parity both before and after diagnosis. Indeed, women with MS have historically been recommended not to become pregnant due to the belief that this might aggravate the course of the disease.[46] Supplementary analyses showed that neither reduced parity nor delayed first child birth could account for the presently observed increased breast cancer risk.

MS is considered to be more frequent in populations of high socioeconomic status,[12] also believed to be afflicted by increased risk of breast cancer,[47,48] prostate cancer[49] and colon cancer.[50] A recent study found no evidence of a socioeconomic gradient in the occurrence of MS in the Danish population[51] and accordingly, we believe that uncontrolled confounding from factors related to socioeconomic status are unlikely to explain the observed cancer profile in MS patients.

Compared to the general population most MS patients will be in closer and more regular contact with general practitioners, hospitals or outpatient clinics, raising the possibility of surveillance bias as explanation for the increased risk of breast cancer. Data from the Danish Breast Cancer Cooperative Group showed, however, that size of the breast tumour at time of diagnosis was larger for women with MS than for other women, suggesting that surveillance bias does not explain our findings.

While we consider it unlikely to account entirely for the observed cancer pattern in the MS cohort, we cannot rule out that diagnostic neglect by the public health care system may have resulted in an underestimation of the number of cancers occurring in the patients. The observation of a larger size of breast cancer tumour at the time of diagnosis in women with MS compared to women without MS would be compatible with such a mechanism.

It has recently been hypothesised that solar radiation protects against MS.[52,53] Under this hypothesis, MS patients should be at reduced risk of skin cancer. In our study, no such decreased risk of skin cancer was observed, rendering little support for a strong role of UV-light in MS development.

Finally, female MS patients were at increased risk of nasopharyngeal cancers (NPC). Although Epstein-Barr Virus has been implicated in both NPC[54] and MS,[55] our observation is based on 2 cases only, and should be interpreted accordingly.

In present nationwide cohort study, we used unique and compatible population-based Danish registers of MS and cancer, together with the Danish Civil Registration System. Both disease registers are characterised by high degrees of validity, completeness and long existence (more than 40 years).[6,20,24] Thus, there is

little evidence to suggest that our findings should be explained by methodological factors related to the study design.

Based on established disease registers, however, we had no access to individual information on potential risk factors such as medication, smoking and diet. Thus we can only examine associations between MS and certain cancer forms and not whether these associations are causal or merely due to confounding by the above factors.

Overall, our study suggests that MS patients are not at increased risk of cancer. Rather for several types of cancer statistically significantly reduced risks were observed. The small increased risk of breast cancer in women with MS, consistent with previous observations, remains unexplained and warrants further attention.

Acknowledgement

The study was approved by the Danish Data Protection Agency (2001-41-0702).

References

1. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med 2000;343:938–52.
2. Kurtzke JF. Epidemiologic evidence for multiple sclerosis as an infection. Clin Microbiol Rev 1993;6:382–427.
3. Weinshenker BG. Epidemiology of multiple sclerosis. Neurol Clin 1996;14:291–308.
4. Wynn DR, Rodriguez M, O'Fallon WM, Kurland LT. A reappraisal of the epidemiology of multiple sclerosis in Olmsted Country Minnesota. Neurology 1990;40:780–6.
5. Barnett MH, Williams DB, Day S, Macaskill P, McLeod JG. Progressive increase in incidence and prevalence of multiple sclerosis in Newcastle, Australia: a 35-year study. J Neurol Sci 2003;213:1–6.
6. Koch-Henriksen N. The Danish Multiple Sclerosis Registry: a 50-year follow-up. Mult Scler 1999;5:293–6.
7. Midgard R, Riise T, Svanes C, Kvale G, Nyland H. Incidence of multiple sclerosis in More and Romsdal, Norway from 1950 to 1991: an age-period-cohort analysis. Brain 1996;119:203–11.
8. Poser S, Stickel B, Krtsch U, Burckhardt D, Nordman B. Increasing incidence of multiple sclerosis in South Lower Saxony, Germany. Neuroepidemiology 1989;8:207–13.
9. Rosati G, Aiello I, Mannu L, Pirastru MI, Agnetti V, Sau G, Garau M, Gioia R, Sanna G. Incidence of multiple sclerosis in the town of Sassari, Sardinia, 1965 to 1985: evidence for increasing occurrence of the disease. Neurology 1988;38:384–8.
10. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. N Engl J Med 2002;347:911–20.
11. Bronnum-Hansen H, Koch-Henriksen N, Stenager E. Trends in survival and cause of death in Danish patients with multiple sclerosis. Brain 2004;11:1–7.
12. Newell GR. Etiology of multiple sclerosis and Hodgkin's disease. Am J Epidemiol 1970;91:119–22.
13. Kurtzke JF, Hamtoft H. Multiple sclerosis and Hodgkin's disease in Denmark. Acta Neurol Scand 1976;53:358–75.
14. Vineis P, Crosignani P, Vigano C, Fontana A, Masala G, Stagnaro E, Miligi L, Costantini AS, Nanni O, Ramazzotti V, Rodella S, Tumino R, et al. Lymphomas and multiple sclerosis in a multicenter case-control study. Epidemiology 2001;12:134–5.
15. Midgard R, Glattre E, Gronning M, Riise T, Edland A, Nyland H. Multiple sclerosis and cancer in Norway: a retrospective cohort study. Acta Neurol Scand 1996;93:411–5.
16. Moller H, Kneller RW, Boice JD, Jr., Olsen JH. Cancer incidence following hospitalization for multiple sclerosis in Denmark. Acta Neurol Scand 1991;84:214–20.
17. Hjalgrim H, Rasmussen S, Rostgaard K, Nielsen NM, Koch-Henriksen N, Munksgaard L, Storm HH, Melbye M. Familial clustering of Hodgkin lymphoma and multiple sclerosis. J Natl Cancer Inst 2004; 96:780–4.
18. Anderson M, Hughes B, Jefferson M, Smith WT, Waterhouse JA. Gliomatous transformation and demyelinating diseases. Brain 1980; 103:603–22.
19. Malig C. The civil registration system in Denmark. Technical Papers 1961;66:1–6.
20. Koch-Henriksen N, Rasmussen S, Stenager E, Madsen M. The Danish Multiple Sclerosis Registry. History, data collection and validity. Dan Med Bull 2001;48:91–4.
21. Allison RS, Millar JH. Prevalence of disseminated sclerosis in Northern Ireland. Ulster Med J 1954;23:1–27.
22. Millar JH, Allison RS. Familial incidence of disseminated sclerosis in Northern Ireland. Ulster Med J 1954;23:29–92.
23. Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, Johnson KP, Sibley WA, Silberberg DH, Tourtellotte WW. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983;13:227–31.
24. Storm HH, Michelsen EV, Clemmensen IH, Pihl J. The Danish Cancer Registry–history, content, quality and use. Dan Med Bull 1997; 44:535–9.
25. Westergaard T, Andersen PK, Pedersen JB, Olsen JH, Frisch M, Sorensen HT, Wohlfahrt J, Melbye M. Birth characteristics, sibling patterns, and acute leukemia risk in childhood: a population-based cohort study. J Natl Cancer Inst 1997;89:939–47.
26. Andersen KW, Mouridsen HT. Danish Breast Cancer Cooperative Group DBCG). A description of the register of the nation-wide programme for primary breast cancer. Acta Oncol 1988;27:627–47.
27. Rostgaard K, Holst H, Mouridsen HT, Lynge E. Do clinical databases render population-based cancer registers obsolete? The example of breast cancer in Denmark. Cancer Causes Control 2000;11:669–74.
28. Thun MJ, Henley SJ, Patrono C. Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues. J Natl Cancer Inst 2002;94:252–66.
29. Sorensen HT, Friis S, Norgard B, Mellemkjaer L, Blot WJ, Mclaughlin JK, Ekbom A, Baron JA. Risk of cancer in a large cohort of nonaspirin NSAID users: a population-based study. Br J Cancer 2003;88: 1687–92.
30. Langman MJ, Cheng KK, Gilman EA, Lancashire RJ. Effect of anti-inflammatory drugs on overall risk of common cancer: case-control study in general practice research database. BMJ 2000;320:1642–6.
31. Schreinemachers DM, Everson RB. Aspirin use and lung, colon, and breast cancer incidence in a prospective study. Epidemiology 1994;5: 138–46.
32. Norrish AE, Jackson RT, McRae CU. Non-steroidal anti-inflammatory drugs and prostate cancer progression. Int J Cancer 1998;77: 511–5.
33. Khuder SA, Mutgi AB. Breast cancer and NSAID use: a meta-analysis. Br J Cancer 2001;84:1188–92.
34. Rosenberg L. Aspirin and breast cancer: no surprises yet. J Natl Cancer Inst 1996;88:941–2.
35. Rosenberg L, Palmer JR, Rao RS, Coogan PF, Strom BL, Zauber AG, Stolley PD, Shapiro S. A case-control study of analgesic use and ovarian cancer. Cancer Epidemiol Biomarkers Prev 2000;9:933–7.
36. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies: Collaborative Group on Hormonal Factors in Breast Cancer. Lancet 1996;347:1713–27.
37. Dixon JM. Hormone replacement therapy and the breast. Surg Oncol 2003;12:251–63.
38. Beral V. Breast cancer and hormone-replacement therapy in the Million Women Study. Lancet 2003;362:419–27.
39. Biglia N, Defabiani E, Ponzone R, Mariani L, Marenco D, Sismondi P. Management of risk of breast carcinoma in postmenopausal women. Endocr Relat Cancer 2004;11:69–83.
40. Diamanti-Kandarakis E. Hormone replacement therapy and risk of malignancy. Curr Opin Obstet Gynecol 2004;16:73–8.
41. Bosetti C, Negri E, Trichopoulos D, Franceschi S, Beral V, Tzonou A, Parazzini F, Greggi S, La Vecchia C. Long-term effects of oral contraceptives on ovarian cancer risk. Int J Cancer 2002;102: 262–5.
42. Jensen GR. Kost og sclerose. 2005 Mar 3.
43. Riboli E, Norat T. Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. Am J Clin Nutr 2003;78:559S–69S.
44. Courville CB, Maschmeyer JE, Delay CP. Effects of smoking on the acute exacerbations of multiple sclerosis. Bull Los Angel Neuro Soc 1964;29:1–6.
45. Kelsey JL, Gammon MD, John EM. Reproductive factors and breast cancer. Epidemiol Rev 1993;15:36–47.
46. Schapira K, Poskanzer DC, Newell DJ, Miller H. Marriage, pregnancy and multiple sclerosis. Brain 1966;89:419–28.
47. Brown J, Harding S, Bethune A, Rosato M. Incidence of health of the nation cancers by social class. Popul Trends 1997;90:40–77.
48. Dano H, Andersen O, Ewertz M, Petersen JH, Lynge E. Socioeconomic status and breast cancer in Denmark. Int J Epidemiol 2003; 32:218–24.
49. Lund Nilsen TI, Johnsen R, Vatten LJ. Socio-economic and lifestyle factors associated with the risk of prostate cancer. Br J Cancer 2000; 82:1358–63.

50. van Loon AJ, Brug J, Goldbohm RA, van den Brandt PA, Burg J. Differences in cancer incidence and mortality among socio-economic groups. Scand J Soc Med 1995;23:110–20.
51. Koch-Henriksen N. An epidemiological study of multiple sclerosis. Familial aggregation social determinants, and exogenic factors. Acta Neurol Scand Suppl 1989;124:1–123.
52. Goldacre MJ, Seagroatt V, Yeates D, Acheson ED. Skin cancer in people with multiple sclerosis: a record linkage study. J Epidemiol Community Health 2004;58:142–4.
53. Freedman DM, Dosemeci M, Alavanja MC. Mortality from multiple sclerosis and exposure to residential and occupational solar radiation: a case-control study based on death certificates. Occup Environ Med 2000;57:418–21.
54. Spano JP, Busson P, Atlan D, Bourhis J, Pignon JP, Esteban C, Armand JP. Nasopharyngeal carcinomas: an update. Eur J Cancer 2003;39:2121–35.
55. Ascherio A, Munch M. Epstein-Barr virus and multiple sclerosis. Epidemiology 2000;11:220–4.