

Familial Clustering of Hodgkin Lymphoma and Multiple Sclerosis

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Background: Epidemiologic similarities between Hodgkin lymphoma in young adults (i.e., between 15 and 44 years old) and multiple sclerosis have led to the suggestion that these diseases may have related etiologies. Previous investigations have not supported this hypothesis, but the negative results could have been caused by methodologic problems. We therefore assessed the risk of developing Hodgkin lymphoma for patients with multiple sclerosis and for their families and the risk of developing multiple sclerosis for patients with Hodgkin lymphoma and for their families. **Methods:** We identified 11 790 patients with multiple sclerosis and 19 599 of their first-degree relatives in Danish population-based registers and followed them for the occurrence of Hodgkin lymphoma. Analogously, we identified 4381 patients with Hodgkin lymphoma and 7388 of their first-degree relatives and followed them for the occurrence of multiple sclerosis. The relative risks (RRs) of Hodgkin lymphoma and multiple sclerosis were expressed as standardized incidence ratios (i.e., the ratio between observed and expected numbers of outcomes based on age, sex, and period-specific incidence rates). All statistical tests were two-sided. **Results:** Overall, six cases of Hodgkin lymphoma were identified in patients with multiple sclerosis (RR for Hodgkin lymphoma = 1.40, 95% confidence interval [CI] = 0.63 to 3.12), two of which occurred in young adults (RR = 1.59, 95% CI = 0.40 to 6.37). The risk of young-adult-onset Hodgkin lymphoma was statistically significantly increased in the first-degree relatives of patients with multiple sclerosis (RR = 1.93, 95% CI = 1.01 to 3.71; n = 9 such lymphomas). Two cases of multiple sclerosis were identified among young adult patients with Hodgkin lymphoma (RR for multiple sclerosis = 0.82, 95% CI = 0.20 to 3.27), and the risk for multiple sclerosis was statistically significantly increased in their first-degree relatives (RR = 2.76, 95% CI = 1.44 to 5.31; n = 9

such multiple sclerosis cases). **Conclusion:** The observed familial clustering of multiple sclerosis and young-adult-onset Hodgkin lymphoma is consistent with the hypothesis that the two conditions share environmental and/or constitutional etiologies. [J Natl Cancer Inst 2004;96:780–4]

The observation that Hodgkin lymphoma and multiple sclerosis shared certain epidemiologic characteristics led Newell (1) to speculate in 1970 that the two conditions are etiologically related. Specifically, Newell noted that multiple sclerosis and Hodgkin lymphoma often have an onset in young adulthood (i.e., between the ages of 15 and 44 years), that both conditions had been epidemiologically associated with socioeconomic affluence, and that both conditions show familial clustering.

Few studies provide information relevant to the hypothesized connection between Hodgkin lymphoma and multiple sclerosis. No geographical correlation between incidence of multiple sclerosis and that of Hodgkin lymphoma was observed in a Danish ecologic study (2). No increase in the co-occurrence of Hodgkin lymphoma and multiple sclerosis in individual patients has been

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reported in follow-up studies with cancer mortality [e.g., *see* (3–5)] or incident cancers (6,7) as outcomes. Finally, no clustering of Hodgkin lymphoma and multiple sclerosis was observed in two case–control studies (8,9), although accumulation of the two conditions within families (including conjugal relatives) was suggested in one study (8). However, inherent methodologic limitations and, in particular, modest numbers of patients in the previous studies make it difficult to rule out the suggested etiologic relationship between Hodgkin lymphoma and multiple sclerosis.

If Hodgkin lymphoma and multiple sclerosis share risk factors, then we would expect both diseases to be found at increased frequency in individuals, in their families, or in both. To investigate this possibility, we took advantage of two unique Danish population-based registers containing information on incident cases of cancer and multiple sclerosis to study the risk of Hodgkin lymphoma in patients with multiple sclerosis and their first-degree relatives and the risk of multiple sclerosis in patients with Hodgkin lymphoma and their first-degree relatives.

MATERIALS AND METHODS

Since April 1, 1968, all Danish citizens have been given a unique 10-digit personal identification number, through which the Danish Civil Registration System continuously monitors their vital status. Starting with persons born in the early 1950s, the Danish Civil Registration System also contains detailed information on family structure that allows it to be used to ascertain individuals' familial relations, i.e., to identify a person's parents, offspring, and siblings (10). The personal identification number is also used in population-based health registers, such as the Danish Cancer Registry and the Danish Multiple Sclerosis Registry, allowing the registers to be linked (11,12).

Cohorts of Patients With Multiple Sclerosis and Their Relatives

The Danish Multiple Sclerosis Registry was officially established in 1956 but actually started operating in 1949 with a nationwide survey of prevalent cases of multiple sclerosis (12). The registration and validation procedures used have ensured high degrees of completeness (>90%) and diagnostic validity (94%) (12). For this study, we identified all persons registered in the Danish Multiple Sclerosis Registry as of December 31, 1997 (most recent year with complete data). We subsequently used the personal identification numbers of all of the patients to identify all their first-degree relatives (parents, siblings, and offspring) recorded in the Danish Civil Registration System.

We followed the cohorts of patients with multiple sclerosis (total = 11 790 patients) and their relatives (total = 19 599 relatives) for diagnoses of Hodgkin lymphoma and (for comparative purposes) for diagnoses of other hematopoietic or lymphatic cancers by linking with the Danish Cancer Registry. Follow-up was from July 1 of the year that multiple sclerosis was diagnosed, date of birth (for patients' relatives), or April 1, 1968, whichever came later, until the date of multiple sclerosis diagnosis (in the relatives), death, emigration, disappearance, or December 31, 1997 (most recent year of complete cancer registration), whichever came first.

Cohorts of Patients With Hodgkin Lymphoma and Their Relatives

The population-based Danish Cancer Registry has been in operation since 1943 (11). The procedures used have ensured that registration is essentially 100% complete for most types of cancer (11). We identified all persons registered with Hodgkin lymphoma in the Danish Cancer Registry between April 1, 1968, and December 31, 1997, and we used their personal identification numbers to identify all their first-degree relatives (parents, siblings, and offspring) recorded in the Danish Civil Registration System.

The cohorts of patients with Hodgkin lymphoma (total = 4381 patients) and their relatives (total = 7388 relatives) were followed in the Danish Multiple Sclerosis Registry for a diagnosis of multiple sclerosis from the date that Hodgkin lymphoma was diagnosed or the date of birth (for patient relatives), whichever came later, until the date that Hodgkin lymphoma was diagnosed (in the relatives), death, emigration, disappearance, or December 31, 1997, whichever came first.

Statistical Analyses

The ratio of the observed to the expected number of outcomes (specific cancer types in the cohorts of patients with multiple sclerosis and their relatives, and multiple sclerosis in the cohorts of patients with Hodgkin lymphoma and their relatives), i.e., the standardized incidence ratio, served as measure of relative risk (RR). The expected numbers of outcomes were estimated by multiplying sex, calendar period, and age-specific (5-year age groups) person-years at risk with correspondingly stratified national population-based incidence rates for the investigated types of cancer and multiple sclerosis. We calculated 95% confidence intervals (CIs) for the relative risks from the Wald test by assuming a Poisson distribution of the observed number of outcomes. All statistical tests were two-sided.

The suspected association between Hodgkin lymphoma and multiple sclerosis rests, among other things, on the frequent onset of disease in young adults (i.e., individuals between the ages of 15 and 44 years) which, for Hodgkin lymphoma, is considered to delineate an epidemiologically meaningful disease entity (13). We therefore conducted additional analyses for Hodgkin lymphoma diagnosed in this specific age interval.

RESULTS

Demographic characteristics of the studied cohorts are presented in Table 1. Because information on family structure can be considered complete only for generations born since the early 1950s, the distribution of identified relatives and their corresponding person-years at risk differ between the parental and offspring generations, with more risk accumulated in the latter.

Hematopoietic and Lymphatic Cancers in Families Afflicted by Multiple Sclerosis

A total of 61 hematopoietic and/or lymphatic cancers were observed among the patients with multiple sclerosis, which corresponded well with the expected number (Table 2). Although slightly more cases than expected of Hodgkin lymphoma and leukemia were observed among the patients with multiple sclerosis, statistically significantly increased risks were not ob-

Table 1. Demographic characteristics of patients with multiple sclerosis or Hodgkin lymphoma and their first-degree relatives, by age group*

Cohort	Patients		Parents		Siblings		Offspring		All relatives	
	No.	Person-years	No.	Person-years	No.	Person-years	No.	Person-years	No.	Person-years
<i>Multiple sclerosis</i>										
Age group										
0–14 y	20	24	0	0	277	961	8026	49 760	8303	50 720
15–34 y	3155	16 962	9	18	2396	14 156	10 934	118 367	13 339	132 541
35–44 y	5701	31 059	306	817	1420	5001	3656	17 315	5382	23 133
≥45 y	9048	105 834	3369	23 182	144	401	305	1078	3818	24 661
All ages	11 790	153 878	3417	24 018	3006	20 519	13 176	186 519	19 599	231 056
<i>Hodgkin lymphoma</i>										
Age group										
0–14 y	147	440	0	0	414	1777	2346	16 941	2760	18 718
15–34 y	1748	11 369	61	168	1513	12 206	2693	26 742	4267	39 116
35–44 y	1511	8562	457	1850	635	2465	897	4054	1989	8369
≥45 y	2759	16 981	1892	17 172	33	47	76	243	2001	17 463
All ages	4381	37 351	1966	19 189	1743	16 495	3679	47 981	7388	83 665

*Demographic characteristics of cohorts of multiple sclerosis patients and their first-degree relatives, with number of persons and person-years at risk overall (all ages) and in different age strata. Note that patients and their relatives may be at risk in more than one age stratum. Numbers may not add up due to rounding.

served for any individual subtype of cancer studied (Table 2). Six cases of Hodgkin lymphoma were observed among patients with multiple sclerosis (RR = 1.40, 95% CI = 0.63 to 3.12), two of which occurred in individuals aged 15–44 years (RR = 1.59, 95% CI = 0.40 to 6.37) (Table 3).

The risk of all types of hematopoietic and lymphatic cancers combined was statistically significantly increased among first-degree relatives of patients with multiple sclerosis (RR = 1.57, 95% CI = 1.18 to 2.09; n = 47). This result reflected increased risks of most of the specific hematopoietic and lymphatic cancer subtypes studied, although a statistically significantly increased risk was observed only for non-Hodgkin lymphoma (Table 2) (RR = 1.93, 95% CI = 1.26 to 2.96; n = 21). The increased risk of non-Hodgkin lymphoma appeared to be particularly prominent in the offspring of patients with multiple sclerosis (RR = 2.35, 95% CI = 1.26 to 4.37; n = 10); however, the risk could be assumed to be uniformly increased in the different groups of relatives ($P_{\text{homogeneity}} = .71$) (Table 2).

The overall risk for Hodgkin lymphoma was increased in the combined group of first-degree relatives of patients with multiple sclerosis, although the increase was not statistically significant (RR = 1.63, 95% CI = 0.85 to 3.13; n = 9) (Table 2). All nine cases of Hodgkin lymphoma occurred in the young-adult age group, for which the increase was statistically significant (RR for young-adult-onset Hodgkin lymphoma = 1.93, 95% CI = 1.01 to 3.71) (Table 3).

Multiple Sclerosis in Families Afflicted by Hodgkin Lymphoma

Two cases of multiple sclerosis were observed in patients with Hodgkin lymphoma compared with 2.86 cases expected (RR = 0.70, 95% CI = 0.17 to 2.80). Both cases occurred in patients diagnosed with young-adult-onset Hodgkin lymphoma (RR = 0.82, 95% CI = 0.20 to 3.27) (Table 3). The risk of multiple sclerosis was increased among the first-degree relatives of patients with Hodgkin lymphoma (RR = 2.25, 95% CI = 1.24 to 4.06; n = 11). Nine of the observed cases of multiple sclerosis occurred in relatives of patients with young-adult-

onset Hodgkin lymphoma (RR = 2.76, 95% CI = 1.44 to 5.31) (Table 3).

DISCUSSION

We used two population-based registers to test the hypothesis that Hodgkin lymphoma and multiple sclerosis share etiologies by assessing whether the two diseases cluster within patients and/or their families. Whereas follow-up of patients with Hodgkin lymphoma and patients with multiple sclerosis provided little evidence of an accumulation of the two conditions within individuals, analyses of the patients' first-degree relatives indicated familial aggregation of Hodgkin lymphoma and multiple sclerosis.

Various mechanisms may explain the observed clustering of the two diseases within families, but we find it unlikely to be a chance phenomenon. Specifically, it is consistent with the proposed hypothesis of a common etiology for the two diseases (1), and the familial clustering of the two conditions was independently observed in analyses of both families afflicted by Hodgkin lymphoma and families afflicted by multiple sclerosis. In comparison, the unremarkable risks of disease observed in patients with multiple sclerosis and patients with Hodgkin lymphoma were based on limited numbers of observations. Furthermore, we cannot rule out that treatment of multiple sclerosis or of Hodgkin lymphoma may have influenced the patients' subsequent risk for the other disease.

The accumulation of young-adult-onset Hodgkin lymphoma and multiple sclerosis within families may reflect the effects of shared environmental or constitutional risk factors for the two diseases or, more likely, a combination of such factors. It is particularly interesting that Epstein-Barr virus (EBV) infection may be implicated in the development of both Hodgkin lymphoma and multiple sclerosis. Elevated levels of anti-EBV antibodies precede diagnosis of Hodgkin lymphoma (14) and of multiple sclerosis (15), and infectious mononucleosis-related EBV infection has been associated with increased risk of both Hodgkin lymphoma (16,17) and multiple sclerosis (18) in young adults.

Table 2. Risk of cancer in multiple sclerosis patients and their relatives*

Cancer type	No. observed	No. expected	RR (95% CI)
All blood cancers			
Multiple sclerosis patients	61	58.44	1.04 (0.81 to 1.34)
All relatives	47	29.94	1.57 (1.18 to 2.09)
Offspring	20	13.35	1.50 (0.97 to 2.32)
Parents	23	14.74	1.56 (1.04 to 2.35)
Siblings	4	1.85	2.16 (0.81 to 5.77)
Non-Hodgkin lymphoma			
Multiple sclerosis patients	20	21.62	0.92 (0.60 to 1.43)
All relatives	21	10.87	1.93 (1.26 to 2.96)
Offspring	10	4.26	2.35 (1.26 to 4.37)
Parents	10	5.83	1.71 (0.92 to 3.19)
Siblings	1	0.78	1.28 (0.18 to 9.09)
Hodgkin lymphoma			
Multiple sclerosis patients	6	4.29	1.40 (0.63 to 3.12)
All relatives	9	5.53	1.63 (0.85 to 3.13)
Offspring	6	4.33	1.39 (0.62 to 3.09)
Parents	0	0.63	—
Siblings	3	0.57	5.22 (1.68 to 16.19)
Multiple myeloma			
Multiple sclerosis patients	7	10.29	0.68 (0.32 to 1.43)
All relatives	4	2.97	1.35 (0.51 to 3.59)
Offspring	0	0.15	—
Parents	4	2.78	1.44 (0.54 to 3.84)
Siblings	0	0.04	—
Leukemia			
Multiple sclerosis patients	27	21.64	1.25 (0.86 to 1.82)
All relatives	13	10.35	1.26 (0.73 to 2.16)
Offspring	4	4.58	0.87 (0.33 to 2.33)
Parents	9	5.32	1.69 (0.88 to 3.25)
Siblings	0	0.45	—
Mycosis fungoides			
Multiple sclerosis patients	1	0.60	1.66 (0.23 to 11.78)
All relatives	0	0.22	—
Offspring	0	0.04	—
Parents	0	0.18	—
Siblings	0	0.00	—

*Observed and expected numbers of hematopoietic and lymphatic cancers in multiple sclerosis patients and their parents, siblings, and offspring and relative risk (RR) with 95% confidence intervals (CIs) by cancer subtype. — = no cases were observed and no attempts were made to estimate the relative risk.

The clustering of Hodgkin lymphoma and multiple sclerosis is unlikely to be merely a consequence of a shared association with socioeconomic status for Hodgkin lymphoma, multiple sclerosis, and infectious mononucleosis (1,17,19). First, in a large Danish survey of patients with multiple sclerosis, no correlation with socioeconomic status was observed (20). Second, a Canadian investigation showed that adopted (i.e., nonbiologic) relatives of patients with multiple sclerosis, unlike biologic relatives, were not at increased risk of multiple sclerosis, suggesting that shared genetic rather than shared socioeconomic characteristics are more critical to the aggregation of multiple sclerosis in families (21). Third, we recently demonstrated that first-degree relatives of Danish patients with infectious mononucleosis were not at increased risk of developing Hodgkin lymphoma as young adults (22).

Smoking may be associated with an increased risk of Hodgkin lymphoma and multiple sclerosis according to some but not all studies, as summarized previously (23,24). Because of the register-based nature of our investigation, we cannot rule out the possibility that smoking may have confounded our analyses. However, we found no evidence of an increased risk of smoking-related cancers in patients with multiple sclerosis or in

Table 3. Risk of young-adult-onset Hodgkin lymphoma (HL) and multiple sclerosis (MS) in families afflicted with multiple sclerosis or young-adult-onset Hodgkin lymphoma, respectively*

Cohort	Outcome/proband's disease	No. with outcome	RR (95% CI)
Patients	MS/HL	2	0.82 (0.20 to 3.27)
	HL/MS	2	1.59 (0.40 to 6.37)
All relatives combined			
	MS/HL	9	2.76 (1.44 to 5.31)
	HL/MS	9	1.93 (1.01 to 3.71)
Parents	MS/HL	2	1.74 (0.43 to 6.94)
	HL/MS	0	—
Siblings	MS/HL	2	1.83 (0.46 to 7.34)
	HL/MS	3	5.34 (1.72 to 16.57)
Offspring	MS/HL	5	4.93 (2.05 to 11.85)
	HL/MS	6	1.47 (0.66 to 3.27)

*Relative risk (RR) of multiple sclerosis in patients with young-adult-onset Hodgkin lymphoma (at age 15–44 years) and their relatives with 95% confidence intervals (CIs) and observed number of cases, and relative risk of young-adult-onset Hodgkin lymphoma (age 15–44 years) in patients with multiple sclerosis and their relatives with 95% CIs and observed number of cases. — = no cases were observed and no attempts were made to estimate the relative risk.

their relatives (data not shown). Therefore, we consider such confounding unlikely to account for our observations.

We speculate, rather, that other mechanisms, possibly of an immunologic nature, account for the observed familial aggregation of young-adult-onset Hodgkin lymphoma and multiple sclerosis. Interestingly, both familial Hodgkin lymphoma and multiple sclerosis have been associated with the HLA-DR2 allele (25,26). Moreover, the association between infectious mononucleosis on the one hand and the risk of Hodgkin lymphoma (16,17) and of multiple sclerosis (18) on the other could suggest that a common genetic and/or immunologic predisposition to the two diseases may be mediated through interaction with environmental risk factors such as EBV infection, as was recently proposed for multiple sclerosis (27).

We used unique and compatible population-based Danish registers of multiple sclerosis and cancer as well as the Danish Civil Registration System in this historical cohort analysis. Both disease registers are characterized by high degrees of validity and completeness (11,12); therefore, we are confident that surveillance bias does not account for our observations. Moreover, we found no unusual overall cancer risk among the relatives of patients with multiple sclerosis in supplemental follow-up analyses (data not shown). We did not validate the diagnoses of the observed cases of Hodgkin lymphoma, but we do not believe that diagnostic misclassification could explain our findings. Although previous incidence rates of Hodgkin lymphoma have been inflated by the erroneous classification of non-Hodgkin lymphomas as Hodgkin lymphomas (28), this problem primarily concerned Hodgkin lymphoma in the elderly and was much less pronounced in young adults (28). In addition, a 1991 survey of 489 Danish patients with Hodgkin lymphoma diagnosed from 1971 through 1983 found that only two (0.4%) cases had originally been erroneously classified as Hodgkin lymphomas (29). Identification of first-degree relatives of a patient with multiple sclerosis or Hodgkin lymphoma in the study was dependent on their being alive as of April 1, 1968 (the starting date of the

Danish Civil Registration System), or later. Because information on familial relations is not available for persons who died before April 1, 1968, we cannot rule out the possibility that survivor bias may have been introduced into our analyses. However, this bias would most likely lead to conservative risk estimates and therefore is not likely to explain the observed association between Hodgkin lymphoma and multiple sclerosis. Similarly, although information on family structure (parents, siblings, and offspring) in the Danish Civil Registration System can be considered complete only for persons born since the early 1950s, we find this restriction unlikely to have introduced biases that would account for our observations.

In addition to the increased risk of Hodgkin lymphoma, we also observed an increased occurrence of non-Hodgkin lymphoma in first-degree relatives of patients with multiple sclerosis. This observation is consistent with that of a previous Italian case-control study, in which a personal or familial history of multiple sclerosis was associated with a 5.0-fold (95% CI = 1.05- to 23.9-fold) increased risk of non-Hodgkin lymphoma (9). The mechanisms underlying this association remain elusive but, given the well-established connection between immune dysfunction, EBV, and the risk of non-Hodgkin lymphoma (30), the association between multiple sclerosis and non-Hodgkin lymphoma may involve an immunologic mechanism similar to that involved in the proposed association between Hodgkin lymphoma and multiple sclerosis.

In conclusion, our study indicates that multiple sclerosis aggregates with young-adult-onset Hodgkin lymphoma and non-Hodgkin lymphoma within families. The mechanisms explaining this phenomenon may involve environmental or constitutional risk factors or most likely both. Our findings should be confirmed in other studies and, if possible, further characterized (e.g., with respect to the EBV status of the observed lymphomas). Regardless, the results of the present investigation support Newell's hypothesis (1) of an etiology common to young-adult-onset Hodgkin lymphoma and multiple sclerosis.

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