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Medical History, Lifestyle, Family History, and Occupational Risk Factors for Mantle Cell Lymphoma: The InterLymph Non-Hodgkin Lymphoma Subtypes Project

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Background The etiology of mantle cell lymphoma (MCL), a distinctive subtype accounting for 2%–10% of all non-Hodgkin lymphoma, is not known.

Methods We investigated associations with self-reported medical history, lifestyle, family history, and occupational risk factors in a pooled analysis of 557 patients with MCL and 13 766 controls from 13 case–control studies in Europe, North America, and Australia. Odds ratios (ORs) and 95% confidence intervals (CIs) associated with each exposure were examined using multivariate logistic regression models.

Results The median age of the MCL patients was 62 years and 76% were men. Risk of MCL was inversely associated with history of hay fever (OR = 0.63, 95% CI = 0.48 to 0.82), and the association was independent of other atopic diseases and allergies. A hematological malignancy among first-degree relatives was associated with a twofold increased risk of MCL (OR = 1.99, 95% CI = 1.39 to 2.84), which was stronger in men (OR = 2.21, 95% CI = 1.44 to 3.38) than women (OR = 1.61, 95% CI = 0.82 to 3.19). A modestly increased risk of MCL was also observed in association with ever having lived on a farm (OR = 1.40, 95% CI = 1.03 to 1.90). Unlike some other non-Hodgkin lymphoma subtypes, MCL risk was not statistically significantly associated with autoimmune disorders, tobacco smoking, alcohol intake, body mass index, or ultraviolet radiation.

Conclusions The novel observations of a possible role for atopy and allergy and farm life in risk of MCL, together with confirmatory evidence of a familial link, suggest a multifactorial etiology of immune-related environmental exposures and genetic susceptibility. These findings provide guidance for future research in MCL etiology.

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Mantle cell lymphoma (MCL) is one of the more recently identified subtypes of non-Hodgkin lymphoma (NHL), formally recognized in 1992 (1) and subsequently adopted into the Revised European-American Lymphoma (REAL) (2) and World Health Organization (WHO) classifications (3,4). MCL accounts for between 2% and 10% of all NHL (5,6). In part due to its recent recognition and uncommon occurrence, epidemiological studies of MCL are few and no specific causes have been confirmed (7,8). MCL is typically diagnosed in those aged 60 years or older, more than twice as often among men than women, and more often among whites than blacks or Asians (9–12). Unlike most NHL subtypes, patients with MCL respond poorly to traditional chemotherapy regimens and the 5-year survival is less than 50% (13). An increasing incidence of MCL over time has been reported in the United States (9,11,14), which could reflect changes in diagnostic practice and the introduction of immunohistochemical staining for cyclin D1 (9) and/or a true increase.

Biologically and clinically distinct features of MCL that may harbor clues to its etiology include a restricted Ig repertoire of the tumor cells and somatic hypermutation (15–17), as well as the frequent involvement of extranodal tissues such as the gastrointestinal (GI) tract (18). Moderate associations with MCL risk have been reported for certain autoimmune disorders (19), family history of hematopoietic malignancy, specifically male relatives (20), and *Borrelia burgdorferi* infection (21). However, the number of MCL patients has mostly been low (<150) in previous etiologic investigations, and these findings remain unconfirmed.

To advance our understanding of the etiology of MCL, we investigated associations with medical history, lifestyle, family history, and occupational risk factors in a pooled analysis of 557 cases and 13 766 controls from 13 case–control studies from Europe, North America, and Australia as part of the International Lymphoma Epidemiology Consortium (InterLymph) NHL Subtypes Project.

Materials and Methods

Study Population

Detailed methodology for the InterLymph NHL Subtypes Project is provided elsewhere in this issue. Studies eligible for inclusion

in this pooled analysis fulfilled the following criteria: 1) case–control design, with incident, histologically confirmed cases of MCL according to the WHO classification; and 2) availability of individual-level data for several risk factors of interest by December 31, 2011. Thirteen studies contributed in total 557 MCL patients and 13 766 controls diagnosed and identified from 1995 to 2008. Seven studies were conducted in North America, five in Europe and one in Australia, and eight were population-based, four were hospital- or clinic-based, and one was partly population-based and partly hospital-based. Most studies excluded individuals with a known history of solid organ transplantation or HIV/AIDS. Contributing studies were approved by local ethics review committees, and all participants provided informed consent before interview.

MCL Subtype Ascertainment and Harmonization

Cases were classified according to the WHO classification (3,4) using guidelines from the InterLymph Pathology Working Group (22,23). Most studies had some form of centralized pathology review by at least one expert hematopathologist. Each participating study's pathology review procedures and rules for MCL classification were reviewed for consistency and comparability by an interdisciplinary team of pathologists and epidemiologists.

Because of the potential for risk factors to differ by the primary site of disease, we further classified the cases according to primary site. Lymphoma sites were categorized as nodal or extranodal (24), and a primary site in the GI tract was specifically noted. Cases with widespread disease, no known primary site, or the primary site listed as bone marrow, blood, or cerebrospinal fluid, were classified as systemic.

Risk Factor Ascertainment and Harmonization

Each study collected data on putative risk factors using a standardized, structured format by in-person or telephone interviews and/or self-administered questionnaires. Risk factors selected for inclusion were the available medical history, lifestyle, family history, and occupational risk factors with data from at least three studies. Centralized harmonization of individual-level, deidentified data from each study was a key element of the project. Details of the data harmonization rules as well as the number of studies that contributed data for each exposure are provided elsewhere in this issue.

Statistical Analysis

Risk of MCL associated with each exposure variable was examined using unconditional logistic regression models adjusted for age at diagnosis or interview, race/ethnicity, sex, and study (basic model). The significance of each association was evaluated by a likelihood ratio test, comparing models with and without the exposure variable of interest, with P values less than .05 identifying putatively influential factors. Individuals with missing data for the exposure variable of interest were excluded. To evaluate heterogeneity of effect among the 13 studies, we performed a separate logistic regression within each study and then quantified the variability of the coefficients by the H statistic (25).

We then examined the relationship between case–control status and each putative risk factor considering possible effect modification and accounting for other potential confounders. To consider effect modification, we repeated the above logistic regression analyses stratified by age, sex, geographical region, study, and study design (ie, population-based vs hospital or clinic-based). To account for other potential confounders, we conducted two analyses. First, we evaluated the risk estimate for each putative risk factor in a series of basic models that adjusted for one other putative risk factor individually. Second, we conducted a single logistic regression analysis including all putative risk factors, including a separate missing category for each variable to ensure that the whole study population was included in the analysis (ie, not dropped due to missing data). Finally, we conducted a forward step-wise logistic regression with all putative risk factors. Results from these multivariate analyses were generally similar to the results adjusted for age, sex, race/ethnicity, and study only, and thus are not presented.

Because controls for most original studies were chosen to frequency match to the age and sex of all original study cases, rather than just MCL, we conducted sensitivity analyses using a subset of controls that were matched by age and sex to the cases with MCL. The results from these sensitivity analyses were very similar to the results obtained using the full set of controls and, thus, we retained the full set of controls for our main analyses to increase statistical power. Analyses were conducted using SAS software, version 9.2 (SAS Institute Inc, Cary, NC).

Results

The median age of the patients was 62 years (range 22–88 years), 94% were white (N = 523), and 74% (N = 412) were men (Table 1). Controls tended to be slightly younger (median 59 years, range 16–98 years) and were less likely to be male (52%) than cases. The case participants were diagnosed between 1995 and 2008 in North America (45%), Northern Europe (47%), Southern Europe (3%), or Australia (4%). Most participants were included in population-based studies (78% of the cases and 70% of the controls). Among patients with information available on stage and sites of disease, 85% (N = 351/413) were diagnosed with stage III/IV disease and 74% (N = 320/432) had either nodal or systemic involvement, whereas 7% (N = 30/432) had primary disease in the GI tract.

A history of any atopic condition was inversely associated with risk of MCL (odds ratio [OR] = 0.74, 95% confidence interval [CI] = 0.61 to 0.89) (Table 2). Furthermore, any specific allergy (against insects, plants, etc.) was inversely associated with risk of MCL (OR = 0.79, 95% CI = 0.63 to 0.98), as was hay fever (OR = 0.63, 95% CI = 0.48 to 0.82). Allergy was correlated with atopy (phi coefficient = 0.72, $P < .0001$) and with hay fever (phi coefficient = 0.45, $P < .0001$). However, the significant inverse association for hay fever remained for individuals with or without a history of other atopic disorders (OR = 0.66, 95% CI = 0.49 to 0.89; OR = 0.55, 95% CI = 0.33 to 0.93, respectively). In contrast, a history of allergy, asthma, eczema, or food allergies per se were inversely associated with MCL risk only in combination with a history of at least one other atopic disorder (Table 2). In multivariate analyses mutually adjusted for concomitant atopic disorders, hay fever, but not any allergy, remained inversely associated with MCL (OR = 0.67, 95% CI = 0.49 to 0.93). The reduced risk of MCL associated with hay fever was observed

Table 1. Characteristics of 557 mantle cell lymphoma cases and 13766 controls included in the InterLymph NHL Subtypes Project

	Controls, No. (%)	Cases, No. (%)
Total	13766 (96.1)	557 (3.9)
Age, y		
<30	769 (5.6)	1 (0.2)
30–39	1133 (8.2)	14 (2.5)
40–49	1974 (14.3)	44 (7.9)
50–59	3323 (24.1)	163 (29.3)
60–69	3835 (27.9)	203 (36.4)
70–79	2474 (18.0)	118 (21.2)
≥80	258 (1.9)	11 (2.0)
Missing	0 (0.0)	3 (0.5)
Sex		
Male	7206 (52.3)	412 (74.0)
Female	6560 (47.7)	145 (26.0)
Race/ethnicity		
White, non-Hispanic	12854 (93.4)	523 (93.9)
Black	199 (1.4)	3 (0.5)
Asian	189 (1.4)	10 (1.8)
Hispanic	121 (0.9)	6 (1.1)
Other/unknown/missing	403 (2.9)	15 (2.7)
Socioeconomic status		
Low	4771 (34.7)	208 (37.3)
Medium	4532 (32.9)	168 (30.2)
High	4216 (30.6)	166 (29.8)
Other/missing	247 (1.8)	15 (2.7)
Region		
North America	5060 (36.8)	253 (45.4)
Northern Europe*	6542 (47.5)	264 (47.4)
Southern Europe†	1470 (10.7)	18 (3.2)
Australia	694 (5.0)	22 (3.9)
Design		
Population-based	9673 (70.3)	435 (78.1)
Hospital-based	4093 (29.7)	122 (21.9)
Lymphoma stage at diagnosis		
N/A (Controls)	23096 (100.0)	0 (0.0)
Stages I–II	—	62 (11.1)
Stages III–IV	—	351 (63.2)
Unknown/unclassifiable	—	143 (25.7)

* Includes Sweden, Denmark, Germany, United Kingdom, Ireland, France, and Czech Republic.

† Includes Spain and Italy.

in both sexes (males: OR = 0.67, 95% CI = 0.49 to 0.92; females: OR = 0.54, 95% CI = 0.32 to 0.90).

Few MCL cases reported a history of any physician-diagnosed autoimmune disorder (Table 2). The most frequently reported autoimmune disorders were psoriasis (3.5%, N = 9) and ulcerative colitis (2.1%, N = 8). Perhaps in part as a result of this low frequency, we did not observe statistically significant risks of MCL with any specific autoimmune disorders, including systemic lupus erythematosus, rheumatoid arthritis, type 1 diabetes, Crohn's disease, ulcerative colitis, or psoriasis, or with autoimmune disorders grouped into B-cell or T-cell–activating diseases (Table 2).

A hematological malignancy among one or more first-degree relatives was associated with a twofold increased risk of MCL (OR = 1.99, 95% CI = 1.39 to 2.84, N = 39) (Table 3). The risk was more pronounced among men (OR = 2.21, 95% CI = 1.44 to 3.38) than women (OR = 1.61, 95% CI = 0.82 to 3.19), and if the relative was male (OR = 2.33, 95% CI = 1.46 to 3.72) rather than female (OR = 1.69, 95% CI = 1.00 to 2.84). The greatest difference in risk estimates were where the patient and the relative were male (OR = 2.48, 95% CI = 1.41 to 4.34) as opposed to both being female (OR = 1.37, 95% CI = 0.49 to 3.84), although none of these differences was statistically significant ($P_{heterogeneity}$ = .41 by sex of the patient; $P_{heterogeneity}$ = .12 by sex of the relative; $P_{heterogeneity}$ = 0.28 by sex of the patient and relative). In an analysis of type of hematological malignancy (restricted to subtypes reported by 10 or more cases), risk of MCL was increased approximately twofold both for those with a family history of NHL or of leukemia.

For farming-related exposures, we observed a 40% increased risk of MCL with ever having lived on a farm (OR = 1.40, 95% CI = 1.03 to 1.90) (Table 4), whereas the risk for working on a farm was not significant (OR = 1.17, 95% CI = 0.85 to 1.61). In the eight studies that contributed complete occupational histories, we observed no association with having worked on a farm regardless of the type of farming (Table 4). Concerning other occupations, an increased risk was noted for electrical and electronics workers (OR = 1.63, 95% CI = 1.09 to 2.44, N = 30) and for drivers that were material-handling equipment operators (OR = 3.05, 95% CI = 1.47 to 6.31, N = 9), although the latter was based on a small number of exposed cases (Table 4). There were also suggestive bordeline increased risks among all drivers and cleaners (Table 4).

Risk of MCL was not associated with height, weight or body mass index, tobacco smoking or alcohol intake among both sexes, or use of hair dyes, oral contraceptives, or hormone replacement therapy, or number of children among women (Table 5). High recreational sun exposure was associated with a statistically significant reduced risk but there was no trend in risk over exposure categories (Table 5). Potential associations with physical activity or young adult body mass index were difficult to evaluate due to a relatively high degree of missing data both by design and report (data not shown).

Observed associations with hay fever, family history, living on a farm, and the specific occupations listed above remained unchanged upon multivariate adjustment, nor was there evidence of effect modification by study design, geographical region, age, or primary GI tract involvement (data not shown). Also, there was no evidence of significant variation in results by study as assessed by the *H* statistic, except for with family history of hematological malignancies in female relatives.

Discussion

In this unique international pooled case–control study of risk factors for MCL, we observed a previously unrecognized strong inverse association with hay fever and risk of MCL. We also report a novel increased risk of MCL associated with ever having lived on a farm. These findings suggest a role for environmental factors in MCL etiology. We confirmed an approximately doubled risk of MCL associated with a family history of hematological malignancy, and further showed that risks were more evident among male patients and when the relatives were male, providing clues for future investigations of underlying genetic susceptibility for MCL.

Previous studies investigating the etiology of MCL are rare, although risk of MCL has sometimes been evaluated in the

Table 2. Risk of mantle cell lymphoma associated with a history of selected atopic and autoimmune disorders*

	Controls, No. (%)†	Cases, No. (%)†	OR (95% CI)	*P*
Atopic disorders				
Any atopic disorder‡				
No	8201 (59.6)	366 (65.7)	1.00 (referent)	.001
Yes	5336 (38.8)	174 (31.2)	0.74 (0.61 to 0.89)	
Allergy§				
No	8227 (66.3)	369 (69.4)	1.00 (referent)	.031
Yes	3312 (26.7)	117 (22.0)	0.79 (0.63 to 0.98)	
Allergy and other atopic conditions				
No	8227 (66.3)	369 (69.4)	1.00 (referent)	.010
Allergy but no other atopic conditions	1065 (8.6)	44 (8.3)	1.05 (0.75 to 1.45)	
Allergy and asthma, hay fever, or eczema	2247 (18.1)	73 (13.7)	0.68 (0.52 to 0.88)	
Asthma				
No	10 939 (80.3)	436 (79.3)	1.00 (referent)	.122
Yes	1197 (8.8)	36 (6.5)	0.77 (0.54 to 1.09)	
Asthma and other atopic conditions				
No	10 939 (80.3)	436 (79.3)	1.00 (referent)	.225
Asthma but no other atopic conditions	435 (3.2)	15 (2.7)	0.90 (0.53 to 1.54)	
Asthma and allergy, hay fever, or eczema	762 (5.6)	21 (3.8)	0.69 (0.44 to 1.08)	
Hay fever				
No	8157 (62.2)	351 (64.1)	1.00 (referent)	<.001
Yes	2727 (20.8)	80 (14.6)	0.63 (0.48 to 0.82)	
Hay fever and other atopic conditions				
No	8157 (62.2)	351 (64.1)	1.00 (referent)	.002
Hay fever but no other atopic conditions	700 (5.3)	16 (2.9)	0.55 (0.33 to 0.93)	
Hay fever and asthma, allergy, or eczema	2027 (15.4)	64 (11.7)	0.66 (0.49 to 0.89)	
Eczema				
No	11 072 (83.5)	478 (86.1)	1.00 (referent)	.304
Yes	1437 (10.8)	43 (7.7)	0.85 (0.61 to 1.17)	
Eczema and other atopic conditions				
No	11 072 (83.5)	478 (86.1)	1.00 (referent)	.567
Eczema but no other atopic conditions	528 (4.0)	16 (2.9)	0.90 (0.54 to 1.50)	
Eczema and allergy, hay fever, or eczema	909 (6.9)	27 (4.9)	0.82 (0.55 to 1.23)	
Food allergy				
No	9988 (80.5)	396 (74.4)	1.00 (referent)	.875
Yes	997 (8.0)	33 (6.2)	0.97 (0.67 to 1.41)	
Food allergy and other atopic conditions				
No	9988 (80.5)	396 (74.4)	1.00 (referent)	.460
Food allergy but no other atopic conditions	403 (3.2)	17 (3.2)	1.23 (0.74 to 2.04)	
Food allergy and asthma, hay fever, or eczema	594 (4.8)	16 (3.0)	0.79 (0.47 to 1.33)	
Autoimmune disorders				
History of autoimmune disease‖				
No autoimmune disease	13 158 (95.6)	531 (95.3)	1.00 (referent)	.846
B-cell activation	125 (0.9)	5 (0.9)	1.11 (0.45 to 2.76)	
T-cell activation	471 (3.4)	21 (3.8)	1.03 (0.65 to 1.62)	
Both	12 (0.1)	0 (0.0)		
Systemic lupus erythematosus				
No	11 065 (98.1)	452 (97.2)	1.00 (referent)	.199
Yes	25 (0.2)	2 (0.4)	3.05 (0.69 to 13.42)	
Rheumatoid arthritis				
No	6368 (89.4)	297 (90.3)	1.00 (referent)	.363
Yes	82 (1.2)	2 (0.6)	0.55 (0.13 to 2.27)	
Type I diabetes				
No	8658 (94.0)	319 (94.1)	1.00 (referent)	.617
Yes	63 (0.7)	2 (0.6)	0.70 (0.16 to 3.04)	
Psoriasis				
No	7333 (96.6)	245 (95.0)	1.00 (referent)	.978
Yes	228 (3.0)	9 (3.5)	0.99 (0.50 to 1.97)	
Crohn's disease				
No	9924 (97.8)	444 (96.9)	1.00 (referent)	.799
Yes	31 (0.3)	2 (0.4)	1.22 (0.28 to 5.31)	

(Table continues)

Table 2 (Continued).

	Controls, No. (%)†	Cases, No. (%)†	OR (95% CI)	*P*
Ulcerative colitis				
No	7777 (96.5)	365 (94.6)	1.00 (referent)	.116
Yes	81 (1.0)	8 (2.1)	1.93 (0.90 to 4.12)	

* Odds ratio (OR) and 95% confidence interval (CI) adjusted for age, sex, race, and study. Physician-diagnosed autoimmune diseases with at least two exposed cases are presented.

† The counts do not add up to the total number of cases and controls due to data missing by design or report.

‡ Atopic disorders include asthma, eczema, hay fever, or other allergies, excluding drug allergies.

§ History of allergy excluded drug allergies, asthma, eczema, and hay fever.

‖ Autoimmune diseases associated with B-cell activation include rheumatoid arthritis, Sjögren syndrome, systemic lupus erythematosus, pernicious anemia, hemolytic anemia, and myasthenia gravis, whereas autoimmune diseases causing T-cell activation include psoriasis, celiac disease, inflammatory bowel disorders, sarcoidosis, multiple sclerosis, polymyositis or dermatomyositis, systemic sclerosis or scleroderma, and type I diabetes.

context of studies of all NHL and its subtypes (7,8). In a previous pooled analysis within the InterLymph consortium, we investigated allergic and atopic disorders as possible risk factors for NHL subtypes, and observed a modest inverse association of specific allergies and hay fever with risk of B-cell NHL overall (26), which is in line with some (27,28), but not all (29–31), studies of allergic disorders and NHL. In the previous InterLymph study, risk of MCL was evaluated together with chronic lymphocytic leukemia and small lymphocytic lymphoma, and nonsignificant inverse associations with atopy and allergy were observed for this mixed group. Concern has been expressed that the reported inverse association between atopy and allergy and NHL or B-cell NHL could be explained by reverse causality due to a dysfunctional immune system and impaired antibody response during the preclinical phase of a B-cell malignancy (29,32). To reduce the risk of this potential bias, reports of the occurrence of atopy and allergy within 2 years before diagnosis or interview were disregarded. Also, our findings of an association specifically with hay fever and MCL risk argues against such an explanation. Hay fever is characterized by a hypersensitive immune response where interaction of IgE antibodies and allergens leads to an abundant release of cytokines and chemokines (33). It has been speculated that this heightened response may also act against cancer-specific or cancer-associated antigens and lead to early detection and eradication of tumor cells (34). Further studies are needed to confirm the observed association and to better understand the potential mechanisms in risk of MCL.

The role of a family history of hematological malignancy and risk of MCL has been investigated once previously (20), and included 40% of the cases in the current study. With more than twice as many patients in the present analysis, we demonstrated a similar, approximately doubled risk of MCL in association with self-reported family history of related malignancies, specifically among male relatives. We also extended the previous investigation in showing that male patients were more likely than females to have a positive family history. Surprisingly, although MCL is a disease that occurs predominantly in males, we did not identify gender-specific risks or indications of effect modification by gender for any other exposure. Our analyses also revealed higher risks when the affected relatives were male, although this observation may be explained by the male predominance of most hematopoietic malignancies.

The most likely biological mechanism behind the observed familial link is inherited genetic variation, although shared environmental factors could also theoretically contribute to risk. A few studies have investigated candidate gene variants and risk of NHL including MCL (35–37), and associations with variants in the proinflammatory tumor necrosis factor and the interleukin 10 genes have been reported, but remain unconfirmed. Based on the familial risk of MCL and the lack of consistent results in previous small-scale candidate gene studies, a large-scale investigation of genetic susceptibility for MCL is warranted. With regard to the pattern of a male predominance in family history and MCL risk, our findings indicate that further investigation of the role of genetic susceptibility in MCL should be stratified by sex.

An array of occupational exposures, including most notably organic solvents and pesticides, have been associated with risk of NHL overall and B-cell NHL (38,39). A history of farming was one of the first risk factors identified for NHL (39,40), but no previous studies have investigated such risks specifically for MCL. Although our data support an association between MCL and living on a farm, the results should be interpreted cautiously in light of the lack of a clear association with working on a farm. Some occupational risk factors have been investigated previously in risk of NHL and its subtypes within the consortium (41), but case numbers did not allow for separate evaluation of risk of MCL. In the current investigation, our results suggest that electric and electronics workers, as well as material-handling operator drivers, may have an increased risk of MCL, although the numbers of exposed cases were small. These occupational groups are highly exposed to engine exhausts, organic solvents and polychlorinated biphenyls, and electric and electronic workers are also exposed to electromagnetic fields (42,43). The lack of association in the current study with other occupations characterized by exposure to similar agents, such as painters, welders, textile, and wood workers, suggests that our positive findings could be due to chance and/or bias and should be interpreted with caution.

Interestingly, risk of MCL was not related to a history of autoimmune disorders or lifestyle factors such as tobacco smoking, alcohol intake, hair dye use, ultraviolet radiation, body mass index, or hormonal factors, in contrast with one or several more common NHL subtypes (44–49). However, associations with specific disorders, such as, for example, ulcerative colitis, cannot be ruled out in view of limited power. We also note that profound immunosuppression (eg, associated with HIV/AIDS or following solid organ transplantation), a well-established risk factor for NHL overall and for specific subtypes such as diffuse large B-cell lymphoma, has not been associated with MCL (14,50).

Table 3. Risk of mantle cell lymphoma associated with a history of hematological malignancy in a first-degree relative, overall and by sex of the patient and the relative*

	Total				Females				Males			
First-degree family history	**Controls†, No. (%)**	**Cases†, No. (%)**	**OR (95% CI)**	***P***	**Controls†, No. (%)**	**Cases†, No. (%)**	**OR (95% CI)**	***P***	**Controls†, No. (%)**	**Cases†, No. (%)**	**OR (95% CI)**	***P***
Any hematologic malignancy												
No	8519 (86.2)	298 (77.0)	1.00 (referent)	<.001	4039 (84.8)	84 (79.2)	1.00 (referent)	.194	4081 (86.2)	214 (76.2)	1.00 (referent)	<.001
Yes	492 (5.0)	39 (10.1)	1.99 (1.39 to 2.84)		267 (5.6)	10 (9.4)	1.61 (0.82 to 3.19)		216 (4.6)	29 (10.3)	2.21 (1.44 to 3.38)	
Any hematologic malignancy, male relative												
No	7940 (88.0)	283 (79.7)	1.00 (referent)	.001	3907 (87.1)	84 (82.4)	1.00 (referent)	.164	3696 (88.1)	199 (78.7)	1.00 (referent)	.004
Yes	230 (2.5)	22 (6.2)	2.33 (1.46 to 3.72)		122 (2.7)	6 (5.9)	1.96 (0.82 to 4.66)		104 (2.5)	16 (6.3)	2.48 (1.41 to 4.34)	
Any hematologic malignancy, female relative												
No	7936 (87.9)	288 (81.1)	1.00 (referent)	.064	3903 (87.0)	86 (84.3)	1.00 (referent)	.571	3695 (88.1)	202 (79.8)	1.00 (referent)	.051
Yes	234 (2.6)	17 (4.8)	1.69 (1.00 to 2.84)		126 (2.8)	4 (3.9)	1.37 (0.49 to 3.84)		105 (2.5)	13 (5.1)	1.92 (1.04 to 3.53)	
NHL†												
No	8085 (88.2)	296 (81.8)	1.00 (referent)	.024	3913 (87.2)	88 (86.3)	1.00 (referent)	.65	3767 (88.5)	208 (80.0)	1.00 (referent)	.005
Yes	205 (2.2)	16 (4.4)	1.95 (1.14 to 3.34)		116 (2.6)	2 (2.0)	0.73 (0.18 to 3.04)		86 (2.0)	14 (5.4)	2.58 (1.41 to 4.71)	
NHL, male relative												
No	8077 (89.5)	295 (83.1)	1.00 (referent)	.009	3977 (88.6)	88 (86.3)	1.00 (referent)	.536	3137 (87.9)	176 (79.3)	1.00 (referent)	.013
Yes	93 (1.0)	10 (2.8)	2.78 (1.40 to 5.52)		52 (1.2)	2 (2.0)	1.64 (0.38 to 7.01)		40 (1.1)	8 (3.6)	3.11 (1.40 to 6.93)	
NHL, female relative												
No	8061 (89.3)	301 (84.8)	1.00 (referent)	.775	3966 (88.4)	90 (88.2)	1.00 (referent)	.09	3754 (89.5)	211 (83.4)	1.00 (referent)	.607
Yes	109 (1.2)	4 (1.1)	0.87 (0.31 to 2.39)		63 (1.4)	0 (0.0)	—		46 (1.1)	4 (1.6)	1.33 (0.47 to 3.81)	
Leukemia†,‡												
No	7930 (87.9)	286 (80.6)	1.00 (referent)	.012	3903 (87.0)	84 (82.4)	1.00 (referent)	.116	3692 (88.0)	202 (79.8)	1.00 (referent)	.036
Yes	240 (2.6)	19 (5.1)	2.01 (1.10 to 3.68)		126 (2.8)	6 (5.9)	2.14 (0.90 to 5.09)		108 (2.6)	13 (5.1)	2.01 (1.10 to 3.68)	
Leukemia, male relative												
No	3743 (89.2)	210 (83.0)	1.00 (referent)	.498	3958 (88.2)	87 (85.3)	1.00 (referent)	.398	3743 (89.2)	210 (83.0)	1.00 (referent)	.498
Yes	131 (1.4)	8 (2.0)	1.40 (0.55 to 3.59)		71 (1.6)	3 (2.9)	1.75 (0.53 to 5.82)		57 (1.4)	5 (2.0)	1.40 (0.55 to 3.59)	
Leukemia, female relative												
No	3750 (89.4)	207 (81.8)	1.00 (referent)	.026	3303 (86.7)	76 (83.5)	1.00 (referent)	.128	3750 (89.4)	207 (81.8)	1.00 (referent)	.026
Yes	103 (1.2)	11 (3.2)	2.66 (1.22 to 5.81)		50 (1.3).	3 (3.3)	2.92 (0.87 to 9.80)		50 (1.2)	8 (3.2)	2.66 (1.22 to 5.81)	

* Odds ratio (OR) and 95% confidence interval (CI) adjusted for age, sex, race, and study. NHL = non-Hodgkin lymphoma.

† The counts do not add up to the total number of cases and controls due to data missing by design or report. Also, male and female counts do not always add up to the total as all studies did not contribute to every analysis.

‡ Based on International Statistical Classification of Diseases and Related Health Problems (ICD)- 9 and ICD10 classification.

Table 4. Risk of mantle cell lymphoma associated with a history of farming and selected occupations*

	Controls, No. (%)†	Cases, No. (%)†	OR (95% CI)	*P*
Farming				
Ever lived or worked on a farm‡				
No	6488 (65.0)	211 (61.3)	1.00 (referent)	.254
Yes	3232 (32.4)	120 (34.9)	1.17 (0.90 to 1.53)	
Ever lived on a farm				
No	3230 (53.1)	99 (46.3)	1.00 (referent)	.031
Yes	2617 (43.0)	102 (47.7)	1.40 (1.03 to 1.90)	
Ever worked on a farm‡				
No	7791 (84.1)	260 (79.3)	1.00 (referent)	.334
Yes	1272 (13.7)	57 (17.4)	1.17 (0.85 to 1.61)	
Ever worked in animal farming				
No	7946 (97.3)	279 (97.6)	1.00 (referent)	.683
Yes	204 (2.5)	7 (2.4)	0.85 (0.39 to 1.86)	
Ever worked in crop farming				
No	7857 (96.2)	276 (96.5)	1.00 (referent)	.695
Yes	293 (3.6)	10 (3.5)	0.87 (0.44 to 1.73)	
Ever worked in field crop and vegetable farming				
No	6639 (97.8)	219 (99.5)	1.00 (referent)	.062
Yes	122 (1.8)	1 (0.5)	0.23 (0.03 to 1.69)	
Ever worked in mixed and unspecified farming				
No	7135 (93.5)	245 (90.7)	1.00 (referent)	.457
Yes	482 (6.3)	25 (9.3)	1.19 (0.76 to 1.84)	
Other occupations				
Cleaners				
No	7746 (94.9)	269 (94.1)	1.00 (referent)	.088
Yes	404 (4.9)	17 (5.9)	1.61 (0.96 to 2.69)	
Drivers				
No	7538 (92.3)	248 (86.7)	1.00 (referent)	.086
Yes	612 (7.5)	38 (13.3)	1.40 (0.97 to 2.03)	
Drivers: material-handling equipment operators				
No	8069 (98.8)	277 (96.9)	1.00 (referent)	.008
Yes	70 (0.9)	9 (3.1)	3.05 (1.47 to 6.31)	
Electrical and electronics workers				
No	7690 (94.2)	256 (89.5)	1.00 (referent)	.023
Yes	460 (5.6)	30 (10.5)	1.63 (1.09 to 2.44)	
Woodworkers				
No	7909 (96.9)	271 (94.8)	1.00 (referent)	.240
Yes	241 (3.0)	15 (5.2)	1.41 (0.81 to 2.43)	
Welders and flamecutters				
No	8017 (98.2)	280 (97.9)	1.00 (referent)	.898
Yes	133 (1.6)	6 (2.1)	1.06 (0.46 to 2.44)	
Textile worker				
No	7724 (94.6)	275 (96.2)	1.00 (referent)	.953
Yes	426 (5.2)	11 (3.8)	1.02 (0.54 to 1.91)	
Painter				
No	8015 (98.2)	278 (97.2)	1.00 (referent)	.396
Yes	135 (1.7)	8 (2.8)	1.39 (0.67 to 2.91)	
Metal worker				
No	7693 (94.2)	267 (93.4)	1.00 (referent)	.709
Yes	457 (5.6)	19 (6.6)	0.91 (0.55 to 1.50)	

* Odds ratio (OR) and 95% confidence interval (95% CI) adjusted for age, sex, race, and study.

† The counts do not add up to the total number of cases and controls due to data missing by design or report.

‡ Indicates self-reported history of living and/or working on a farm, based on specific questions during interview. All other occupational data were ascertained through detailed occupational histories, coded according to the International Standard Classification of Occupations (ISCO), Revised Edition 1968.

In our study, 7% of individuals with MCL had evidence of primary GI tract disease at diagnosis, in line with a recent US registry analysis showing that 7.8% of individuals presented with MCL in a primary GI site (51). Due to the limited number of patients with primary GI MCL, we could not fully evaluate whether risks for MCL differ by primary site of presentation. A previous Scandinavian study suggested that infection with the spirochete *B. burgdorferi* increased MCL risk (21). However, those findings have so far not been validated nor refuted by others. Irrespective of the scarce evidence for associations between specific infectious agents and MCL, a role for antigenic drive in the etiology of at least a subset of MCL is supported by findings of a restricted Ig gene repertoire and targeted somatic hypermutation in MCL tumors (15).

Table 5. Risk of mantle cell lymphoma associated with lifestyle factors*

	Controls, No. (%)†	Cases, No. (%)†	OR (95% CI)	*P*
Usual adult BMI, kg/m^2				
15–<18.5	197 (1.5)	4 (0.7)	0.87 (0.31 to 2.44)	
18.5–<22.5	2348 (18.0)	70 (13.1)	1.00 (referent)	.993
22.5–<25	3024 (23.1)	123 (23.0)	1.03 (0.76 to 1.40)	
25–<30	4755 (36.4)	228 (42.6)	1.03 (0.78 to 1.37)	
30–<35	1564 (12.0)	66 (12.3)	0.95 (0.67 to 1.36)	
35–50	582 (4.5)	24 (4.5)	1.05 (0.65 to 1.71)	
Usual adult weight, kg‡				
Quartile 1 (low)	2775 (21.2)	103 (19.3)	1.00 (referent)	.565
Quartile 2	2713 (20.8)	99 (18.5)	0.85 (0.64 to 1.14)	
Quartile 3	3391 (25.9)	150 (28.0)	1.02 (0.78 to 1.32)	
Quartile 4 (high)	3591 (27.5)	163 (30.5)	0.98 (0.76 to 1.28)	
Usual adult height, cm‡				
Quartile 1 (low)	3090 (23.6)	120 (22.4)	1.00 (referent)	.292
Quartile 2	3044 (23.3)	107 (20.0)	0.90 (0.68 to 1.18)	
Quartile 3	3134 (24.0)	149 (27.9)	1.12 (0.86 to 1.44)	
Quartile 4 (high)	3202 (24.5)	139 (26.0)	1.12 (0.86 to 1.46)	
History of cigarette smoking§				
No	5463 (42.3)	183 (36.1)	1.00 (referent)	.598
Yes	6531 (50.5)	273 (53.8)	1.06 (0.87 to 1.29)	
Frequency of cigarette smoking				
Nonsmoker	5463 (42.3)	183 (36.1)	1.00 (referent)	.489
Smoker, 1–10 cigarettes/d	2458 (19.0)	88 (17.4)	1.00 (0.77 to 1.30)	
Smoker, 11–20 cigarettes/d	2647 (20.5)	127 (25.0)	1.17 (0.92 to 1.48)	
Smoker, 21–30 cigarettes/d	622 (4.8)	28 (5.5)	1.14 (0.75 to 1.74)	
Smoker, >30 cigarettes/d	573 (4.4)	21 (4.1)	0.75 (0.47 to 1.20)	
Smoker, cigarettes/d unknown	231 (1.8)	9 (1.8)	0.98 (0.49 to 1.96)	
History of alcohol consumption				
Nondrinker	2121 (17.3)	62 (12.8)	1.00 (referent)	.965
Drinker (at least 1 drink per month)	5717 (46.8)	221 (45.6)	0.99 (0.72 to 1.36)	
Servings of alcohol per week as an adult				
Nondrinker	2121 (17.3)	62 (12.8)	1.00 (referent)	.226
<1 drink/wk	815 (6.7)	18 (3.7)	0.6 (0.35 to 1.04)	
1–6 drinks/wk	2181 (17.8)	85 (17.5)	1.03 (0.72 to 1.47)	
7–13 drinks/wk	1109 (9.1)	53 (10.9)	1.21 (0.81 to 1.82)	
14–27 drinks/wk	947 (7.7)	45 (9.3)	1.14 (0.74 to 1.75)	
28+ drinks/wk or binge drinkers	636 (5.2)	20 (4.1)	0.92 (0.53 to 1.61)	
Drinker, drinks/wk unknown	29 (0.2)	0 (0.0)	—	
Total sun exposure (h/wk)†				
Quartile 1 (low)	1508 (18.7)	44 (16.1)	1.00 (referent)	.428
Quartile 2	1594 (19.8)	42 (15.3)	0.79 (0.51 to 1.22)	
Quartile 3	1633 (20.3)	44 (16.1)	0.73 (0.47 to 1.13)	
Quartile 4 (high)	1714 (21.3)	55 (20.1)	0.72 (0.47 to 1.09)	
Recreational sun exposure (h/wk)†				
Quartile 1 (low)	2234 (20.6)	93 (22.2)	1.00 (referent)	.133
Quartile 2	2332 (21.6)	85 (20.3)	0.92 (0.69 to 1.27)	
Quartile 3	2159 (20.0)	89 (21.3)	0.98 (0.73 to 1.34)	
Quartile 4 (high)	2983 (27.6)	103 (24.6)	0.74 (0.55 to 0.99)	
Ever used hair dyes (women only)				
Never	856 (13.5)	15 (6.7)	1.00 (referent)	.517
Ever	2412 (38.1)	53 (23.7)	1.21 (0.67 to 2.19)	
Frequency of hair dye use (women only)				
Never	856 (13.5)	15 (6.7)	1.00 (referent)	.507
1–5 times/y	835 (13.2)	13 (5.8)	0.94 (0.43 to 2.03)	
6–11 times/y	849 (13.4)	19 (8.5)	1.12 (0.55 to 2.25)	
12+ times/y	507 (8.0)	16 (7.1)	1.77 (0.86 to 3.65)	
Ever, frequency unknown	221 (3.5)	5 (2.2)	1.13 (0.37 to 3.49)	
Number of children (women only)				
0	663 (7.7)	11 (3.7)	0.79 (0.33 to 1.86)	
1	467 (5.5)	11 (3.7)	1.00 (referent)	.820
2	1137 (13.3)	28 (9.4)	0.86 (0.42 to 1.75)	
3+	1541 (18)	28 (9.4)	0.61 (0.29 to 1.26)	

(Table continues)

Table 5 (Continued).

	Controls, No. (%)†	Cases, No. (%)†	OR (95% CI)	*P*
Use of oral contraceptives (women only)				
Never	1871 (32)	39 (20.4)	1.00 (referent)	.805
Ever	1012 (17.3)	18 (9.4)	0.91 (0.45 to 1.85)	
Use of hormone replacement therapy (women only)				
Never	1411 (31.2)	25 (15.2)	1.00 (referent)	.313
Ever	729 (16.1)	22 (13.4)	1.39 (0.74 to 2.62)	

* Odds ratio (OR) and 95% confidence interval (CI) adjusted for age, sex, race, and study. BMI = body mass index.

† The counts do not always add up to the total number of cases and controls due to data missing by design or report.

‡ For height and weight, quartiles were sex-specific, based on the full control population (height, males: <172.0, 172.0–177.7, 177.8–181.9, ≥182.0 cm; females: <159.0, 159.0–162.9, 163.0–167.9, ≥168.0 cm; weight, males: <72.6, 72.6–79.9, 80.0–88.9, ≥89.0 kg; females: <58.1, 58.1–64.9, 65.0–74.7, ≥74.8 kg). For total and recreational sun exposure, study-specific quartiles are available upon request.

§ Smoked longer than 6 mo or more than 100 cigarettes in lifetime.

The strengths of the current study include its large size and the lack of heterogeneity of the results across participating studies in spite of data pooling across several study centers and geographical regions. The most important limitation is the exposure assessment through self-reports, which may be subject to misclassification. In particular, self-reported family history of malignancies may be subject to differential recall among cases and controls, which could have inflated some estimates (52). However, recall bias would not explain the observed differences in results by sex. Also, some results may have arisen by chance considering the large number of analyses performed.

In summary, in this unique international collaborative effort, we provide novel and important leads for future studies of environmental and genetic risk factors in MCL etiology.

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